FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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ARTHRITIS ADVISORY COMMITTEE

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OPEN PUBLIC HEARING

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TUESDAY,

DECEMBER 1, 1998

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The hearing commenced at 8:00 a.m. in the Town Center Hotel at 8727 Colesville Road, Silver Spring, Maryland, Dr. Steven Abramson, Acting Chair, presiding.

MEMBERS PRESENT:

STEVEN B. ABRAMSON, M.D.
FELIX FERNANDEZ-MADRID, M.D., Ph.D.
E NIGEL HARRIS, M.D.
MATTHEW H. LIANG, M.D., M.P.H.
DANIEL J. LOVELL, M.D., M.P.H.
LEONA M. MALONE
KEVIN R. MCCONNELL, M.D.
FRANK PUCINO, JR., Pharm.D.
BARBARA C. TILLEY, Ph.D.

ALSO PRESENT:

DENIS M. MCCARTHY, M.D.
KATHLEEN R. REEDY
EARL D. SILVERMAN, M.D.,FRCPC

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

2 (8:05 a.m.)

3 CHAIRMAN ABRAMSON: I would like to call
4 this meeting to order this morning. I am Steve
5 Abramson from the Hospital for Joint Diseases, New
6 York University. I would like to go around the table
7 and have the members introduce themselves and their
8 institutions.

9 DR. SILVERMAN: Earl Silverman, Hospital
10 for Sick Children, Toronto.

11 DR. MCCARTHY: Denis McCarthy, University
12 of New Mexico, Albuquerque.

13 DR. MCCONNELL: Kevin McConnell,
14 Charlottesville, Virginia.

15 DR. LIANG: Matthew Liang, Brigham and
16 Women's Hospital.

17 MS. MALONE: Leona Malone, Consumer
18 Representative.

19 DR. HARRIS: Nigel Harris, Dean at
20 Morehouse School of Medicine.

21 DR. FERNANDEZ-MADRID: Felix Fernandez-
22 Madrid, Wayne State University.

23 DR. LOVELL: Dan Lovell, University of
24 Cincinnati.

25 MS. REEDY: Kathleen Reedy, Food and Drug

1 Administration.

2 DR. PUCINO: Frank Pucino, National

3 Institutes of Health.

4 DR. LEE: Sue-Chih Lee, Food and Drug

5 Administration.

6 DR. YANG: Josie Yang, Food and Drug

7 Administration.

8 DR. GOLDKIND: Larry Goldkind, Food and

9 Drug Administration.

10 DR. THROCKMORTON: Douglas Throckmorton,

11 Food and Drug Administration.

12 DR. AVERBUCH: Mordechai Averbuch, FDA.

13 DR. WITTER: Jim Witter, FDA.

14 DR. HYDE: John Hyde, FDA.

15 DR. DELAP: Robert DeLap, FDA.

16 CHAIRMAN ABRAMSON: Thank you. We now

17 have a meeting statement from Kathleen Reedy.

18 MS. REEDY: A conflict of interest

19 statement for the Arthritis Advisory Committee

20 Meeting, December 1, 1998, Open Session. The

21 following announcement addresses the issue of conflict

22 of interest with regard to this meeting and is made a

23 part of the record to preclude even the appearance of

24 such at this meeting. Based on the submitted agenda

25 for the meeting and all financial interests reported

1 by the Committee participants, it has been determined
2 that all interests in firms regulated by the Center
3 for Drug Evaluation and Research present no potential
4 for an appearance of a conflict of interest at this
5 meeting with the following exception. In accordance
6 with 18 United States Code 208(b)(3), full waivers
7 have been granted to Dr. Steven Abramson, Dr. Daniel
8 Lovell, and Dr. Matthew Liang, which permits them to
9 participate in all official matters concerning
10 Celebrex. A copy of the waiver statements may be
11 obtained by submitting a written request to the
12 Agency's Freedom of Information Office, Room 12A30 of
13 the Parklawn Building.
14 With respect to FDA's invited guest
15 speakers, Dr. Denis McCarthy and Dr. Earl Silverman
16 have reported interests which we believe should be
17 made public to allow participants to objectively
18 evaluate their comments. Dr. McCarthy would like to
19 disclose that he is involved in a clinical trial
20 sponsored by Wyeth-Ayerst. He is also an occasional
21 consultant to Bohringer Ingolheim, SmithKline Beecham,
22 Wyeth-Ayerst and Merck on arthritis-related drugs and
23 scientific advisory boards.
24 In addition, Dr. Silverman would like to
25 disclose that he owns a small amount of stock in

1 Immunex. In the event that the discussions involve
2 any other products or firms not already on the agenda
3 for which an FDA participant has a financial interest,
4 the participants are aware of the need to exclude
5 themselves from such involvement and their exclusion
6 will be noted for the record. With respect to all
7 other participants, we ask in the interest of fairness
8 that they address any current or previous financial
9 involvement with any firm whose products they may wish
10 to comment upon. That is all.
11 CHAIRMAN ABRAMSON: Thank you. I would
12 now like to ask Dr. DeLap or Dr. Hyde if they would
13 like to make any introductory comments.
14 DR. DELAP: I would just like to say good
15 morning and welcome and thank you all for attending
16 this morning. The advisory committee process is very
17 important to us as a way of obtaining not only expert
18 input into our work processes but also public input.
19 We appreciate very much the work that our sponsors put
20 in in preparing for these meetings. We understand how
21 big an effort that is and sometimes how stressful it
22 can be. We also very much appreciate the time and
23 effort that is put in by the members of our advisory
24 committee. We understand that they always have
25 multiple other commitments and responsibilities, and

1 this is just one more thing sometimes. But we have
2 been very appreciative of their work. Again, we
3 appreciate all of your attendance today. With that,
4 I will turn it over to Dr. Hyde for some additional
5 comments.
6 DR. HYDE: Thank you. I think it is safe
7 to say that 1998 has been an eventful year for
8 rheumatology pharmacotherapy. In September, we had
9 the approval of Araiva. Just last month Enril was
10 approved. And today, in the last month of the year,
11 we are asking you to consider for the first time a
12 COX-2 selective agent that has been developed in the
13 background of our deeper understanding of the
14 Cyclooxygenase enzyme system.
15 I think you will agree with me that this
16 is an information-rich NDA, and Searle is to be
17 commended for their thorough and coherent development
18 program that I think has gone a long way towards
19 answering some of the questions about what COX-2
20 selectivity might mean for clinical medicine. But I
21 would also like to recognize the efforts of the FDA
22 review team, which also includes a GI and a renal
23 consultant from two other FDA review divisions. You
24 will see presentations from most of the reviewers
25 today, but there are many others who have worked on

1 this as well -- project managers, chemists, and team
2 leaders and support staff. All of them have really
3 put in a remarkable effort over the last four to five
4 months to review this massive NDA and to prepare for
5 the advisory committee meeting today. And many of
6 them as well have put in considerable effort in
7 addressing the scientific and regulatory issues of
8 these agents really for the past several years.
9 Just a standard disclaimer, although we
10 are going to present a large body of scientific
11 information from the NDA today, there are also some
12 technical and administrative issues that is our usual
13 practice we aren't presenting to you today. I am just
14 saying that because although the advisory committee is
15 an important part and a milestone in the review
16 process, it is not the conclusion of the review
17 process, and the timing and nature of any final action
18 is going to depend on the entirety of the submission.
19 Now just as I presume we all had a lot on
20 our plates last Thursday, we have got a lot on our
21 plate today. So I will conclude my remarks and hand
22 the meeting back Mr. Chairman.
23 CHAIRMAN ABRAMSON: Thank you very much.
24 We are now about to begin the presentation by Searle.
25 I would just say that the ground rules for the

1 presentations is that we would like to have the
2 presenters make their presentations and the panel can
3 ask questions primarily for clarifying content in this
4 period and not to raise issues that we might want to
5 discuss later in the open discussion period. So if we
6 may begin -- Dr. Needleman, would you like to begin
7 the presentation?
8 DR. SPIVEY: Good morning. My name is
9 Richard Spivey, and I am head of the Regulatory
10 Affairs Department at Searle. Members of the advisory
11 committee and their consultants, colleagues at FDA,
12 and members of the audience, it is indeed my pleasure
13 to begin the review of Celebrex in this public forum.
14 This NDA submitted early this year requests approval
15 for the indications acute or chronic use in the
16 treatment of the signs and symptoms of osteoarthritis
17 and rheumatoid arthritis and management of pain.
18 We will spend about one and a half hours
19 reviewing our development program for Celebrex and the
20 data that was collected in the various studies. Dr.
21 Needleman will provide an overview of the science and
22 rationale for the development of Celecoxib. Dr. Peter
23 Isakson will then review the discovery and preclinical
24 development data, followed by Dr. Aziz Karim. Dr.
25 Karim will review human pharmacokinetics and drug

1 interactions. Dr. Steve Geis will then review the
2 clinical data including clinical efficacy and safety
3 in the proposed indications. He will also review data
4 derived from clinical studies which address areas of
5 uniqueness or differentiation from existing treatment,
6 specifically NSAIDS.
7 As was mentioned by the Chairman, we would
8 like to finish our presentation and limit questions to
9 those of clarification. Once the presentations are
10 concluded, we stand ready to address any specific
11 questions the committee might have. In addition to
12 representatives from Searle, we have several expert
13 consultants in attendance. If any of these experts
14 come to the podium to address specific issues, they
15 will be introduced at that time.
16 We intend to demonstrate through review of
17 our data that Celecoxib is effective in treating
18 osteoarthritis, rheumatoid arthritis and pain. In
19 osteoarthritis, Celecoxib given once daily or in
20 divided doses is equally effective. Celecoxib is a
21 specific COX-2 inhibitor that has an improved safety
22 profile compared to mixed COX-1/COX-2 inhibitors. And
23 finally the clinically significant differences in GI
24 effects compared to NSAIDS warrants specific changes
25 in the NSAID GI class labeling.

1 I will now turn the podium over to Dr.
2 Philip Needleman, who is President of Research and
3 Development at Searle and Chief Science Officer at
4 Monsanto. He will provide an overview of the
5 scientific rationale for the development of Celebrex.
6 Dr. Needleman?
7 DR. NEEDLEMAN: Good morning. It is a
8 particular pleasure for us to be here today because we
9 watched from the birth of the concept of the COX-2
10 inhibitors in our laboratories to the fruition and
11 completion of a major clinical trial. The roots of
12 today's discussion really arise out of the fact that
13 aspirin emerged 100 years ago and a whole family of
14 related non-steroid anti-inflammatories for the
15 treatment of inflammation and pain and ultimately
16 arthritis. It took more than 70 years before John
17 Vane indeed did decisive work in 1971, where he showed
18 that there was a direct temporal and concentration-
19 dependent relationship between the relief of the
20 symptoms of inflammation and the reduction of
21 prostaglandins at the sites of inflammation.
22 Also noted at that time was that there was
23 also a concentration-dependent destruction of all
24 prostaglandin production, including in the desirable
25 sites of prostaglandins such as in the maintenance of

1 the mucosa of the gastrointestinal tract and in
2 platelet function. So indeed the roots of the agents
3 that have been used for over 100 years have had a
4 mechanism-based side effect all due to the fact that
5 they all inhibited prostaglandin.
6 We spent much of the decade of the 1980's
7 in understanding the mechanisms underlying
8 inflammation, and we made a clear observation that in
9 chronic tissue injury there was a massive production
10 of prostaglandin and it was associated with the
11 induction of new cyclooxygenase activity and mass. We
12 further then discovered that steroids,
13 glucocorticoids, suppressed the induced prostaglandin
14 production but not the basal prostaglandin production.
15 That work and work by others led us in 1990 to advance
16 this hypothesis which said that indeed there must be
17 two isoforms of cyclooxygenase. One which we termed
18 COX-1 is the housekeeping enzyme which is maintaining
19 the normal function in the stomach and in the kidney
20 and in the platelets and which is not suppressible by
21 glucocorticoids. A second enzyme, a uniquely induced
22 enzyme as we thought in 1990, we named COX-2. And we
23 found that that was tied to inflammatory injury and to
24 cytokines and that glucocorticoids only block the
25 newly discovered COX-2, but it did that without effect

1 on basal prostaglandin production.

2 And the last element of the 1990

3 hypothesis that we put forward was that all of the

4 existing non-steroid anti-inflammatory agents are non-

5 specific. They inhibit both COX-2 and COX-1. So

6 inherently, you would have mechanism-based side

7 effects while you had the treatment of the

8 inflammatory site. I want to emphasize that all of

9 the existing NSAIDS inhibited COX-2 and COX-1, and you

10 will see that they were quite similarly effective. So

11 in fact, there is a long history in millions of

12 patients for numbers of years of having COX-2

13 inhibition.

14 Based on this hypothesis, in the 1990's we

15 amassed the research enterprise to test the

16 hypothesis. And from that hypothesis, we really began

17 to turn towards not empirical development of agents

18 but rational, mechanism-based drug-targeting of unique

19 drugs that could be directed at COX-2 and spare COX-1.

20 In the preclinical presentation, you will see the

21 evidence that demonstrates that it is, in fact, COX-2,

22 not COX-1, which is the basis of the inflammation and

23 the pain and the swelling in animal models of edema,

24 and that you will see in corollary then the work in

25 preclinical to demonstrate that it is effective in

1 arthritis and pain.

2 Based on the existence of COX-2, we then
3 developed specific COX-2 inhibitors that could go
4 after these rational drug targets but be devoid and
5 spare COX-1 activity.

6 The final point I would like to make is
7 that this is indeed a new class of agents, and you
8 will see -- and it won't be presented here, but you
9 should be aware that COX-2 may well be a major
10 participant or smoking gun in a number of diseases.
11 We already have IND's and clinical trials underway in
12 colon cancer, where it is quite clear from the
13 epidemiology that that is a major driver of the
14 disease and Alzheimer's. So we are pleased to present
15 this, which we believe is a new class of therapeutic
16 agents. I will now turn the rostrum, unless there are
17 questions, to Peter Isakson.

18 DR. ISAKSON: Thanks, Phil. It was
19 evident from the discovery of this enzyme that was
20 closely linked to inflammation that COX-2 provided a
21 well-defined molecular target for rational drug
22 development. In 1992 then, we at Searle began the
23 search for an inhibitor or a compound that was
24 targeted to COX-2. Now our hypothesis at that time
25 was that if we could find such an agent that it would

1 deliver the efficacy of a nonsteroidal -- all of the
2 efficacy there, but could remove or eliminate the side
3 effects that are mechanism-based and associated with
4 the non-steroidals. And noteworthy is that the
5 NSAIDS, though powerful drugs in and of themselves,
6 have essentially no therapeutic index. That is, their
7 side effects occur at the same doses that we achieve
8 efficacy.
9 If we validated this hypothesis then, we
10 would change the paradigm and we would have a new
11 class of drugs that would actually have a clear
12 therapeutic index.
13 Well, in addition to looking for that
14 specifically targeted inhibitor, we had a number of
15 scientific objectives that we wanted to achieve during
16 the course of this development program. It was very
17 important that specific inhibitors, once identified,
18 that we understand the molecular basis for their
19 selectivity. As we moved through the development
20 program, we continually probed this hypothesis. As
21 new data became apparent, we asked where in fact we
22 needed to modify it and where in fact it was correct.
23 And finally, of course, the molecule that we selected
24 needed to demonstrate the efficacy and importantly the
25 safety profile that was consistent with that

1 mechanism, and then we could go forward into clinical
2 evaluation.
3 Well, the foundation for our drug
4 discovery efforts as well as many others was the
5 ability to have recombinant cloned human enzymes that
6 we could assess compounds with in an in-vitro assay.
7 We utilized this kind of a screening tool to assess
8 over 2,000 compounds before we chose Celecoxib. Now
9 this assay is important because it is the one way that
10 we can assess the activity of a compound under
11 identical conditions on the two different isoforms,
12 and it is the one assay that tells us something about
13 the intrinsic avidity of a compound for each enzyme.
14 An example is shown here of Naproxen, of course a
15 widely used nonsteroidal, which shows concentration-
16 dependent inhibition of both isoforms, both human COX-
17 1 and COX-2.
18 Similarly, Ibuprofen, another very widely
19 used non-steroidal, though less potent, shows
20 inhibition of both COX-1 and COX-2.
21 Now in contrast, Celecoxib, the compound
22 we will be discussing today, shows a rather different
23 pattern. That is, it shows potent concentration-
24 dependent inhibition of COX-2, and if full inhibition
25 is achieved orders of magnitude lower than is

1 necessary to inhibit COX-1. Now in our evaluations,
2 it was important to have some way of comparing the
3 activity on those two enzymes. The way we do that and
4 as typically used in the literature is what we call an
5 IC_{50}, which is simply the concentration at which half-
6 maximal inhibition of either isoform is achieved. And
7 that gives us a semiquantitative way of measuring the
8 activity of a compound on either isoform.
9 Using this kind of an analysis, we have
10 looked at all of the non-steroidals, some of which are
11 shown in this table, and we can take those IC_{50} values
12 and make a ratio, which is a convenient way of looking
13 at the world. And what we find is that the non-
14 steroidals are all mixed COX-1 and COX-2 inhibitors
15 that show no specificity for COX-2. So in the order
16 of less than one to three in this particular analysis.
17 Now by contrast, Celecoxib, again based on
18 those concentration curves I showed previously,
19 demonstrates something on the order of 400-fold
20 selectivity for COX-2. And at the beginning of the
21 program, we expected that a difference of on the order
22 of 100 to 1000-fold would be necessary to actually
23 show any kind of a clear therapeutic benefit in the
24 clinic, and Celecoxib then has that range.
25 Well, as I said, it was important to

1 understand the mechanism by which Celecoxib bound, and
2 through x-ray crystallography, we were able to
3 actually visualize that mechanism. What I am showing
4 here are the active sites of COX-1 and COX-2. In this
5 case, flurbiprofen is bound to the active site of COX-
6 1, and Celecoxib we know now actually does bind to the
7 active site of COX-2. Why is it specific? Well, that
8 specificity is actually engendered by the presence of
9 a side pocket in COX-2 shown by this red hatching that
10 in fact is not present in COX-1. And it is this
11 ability to bind or to grasp into this side pocket that
12 allows Celecoxib to be selective.
13 Well, that side pocket which is unique to
14 COX-2 then creates a kinetic mechanism then that we
15 can analyze in great detail. I won't show you or
16 discuss the details of that binding, but suffice it to
17 say we achieved very high affinity binding of COX-2
18 with Celecoxib. And there is one important kinetic
19 characteristic that I want to mention, and that is
20 that the binding -- that once it occurs, it is very
21 slowly reversible. It is not covalent, but it is
22 slowly reversible. And what that translates into is
23 the potential for a duration of action that is, in
24 fact, longer than the pharmacokinetic half-life. In
25 other words, the enzyme is charged with inhibitor even

1 though the drug may have left the circulation.

2 Well, we have also looked at cell-based

3 assays for specificity, and I will show you that.

4 First, this gives you an idea of the action of the

5 drug in a more physiological milieu. In fact, with

6 platelets we can look very early at the specificity of

7 a compound such as Celecoxib, and that is because

8 platelets express only COX-1, and we can initiate

9 production of COX-1 related products then in-vitro.

10 So in this example, we can take human subjects dosed

11 with drug, isolate platelets, and then assess

12 aggregation in-vivo. Now we typically show

13 aggregation that is initiated by arachidonate acid,

14 the substrate for the enzyme, because that gives us

15 the most specific measure of COX-1 activity of a

16 compound. There are many other ways to initiate

17 aggregation, but not all are totally dependent on COX-

18 1.

19 Now alternatively, we can take from the

20 same or other patient's blood and allow it to clot in-

21 vitro. And during the clotting process, massive

22 amounts of thromboxine are released, again by a COX-1

23 in platelets, and this can be readily assessed by

24 measuring serum thromboxine B_2.

25 Finally, in some studies we have measured

1 bleeding time, which we know that the non-steroidals
2 will cause a small increase in that, but that is
3 really a much less sensitive measure of the effect of
4 the drug on COX-1. We initiated such a study, and I
5 will show you first a single dose study where
6 Celecoxib was administered to volunteers at 100, 400,
7 and 800 mg single dose and compared to Ibuprofen. Now
8 when measuring platelet aggregation, we see clear
9 inhibition with Ibuprofen and no inhibition at all
10 with Celecoxib.
11 In the same experiment then or the same
12 study, we looked at serum Thromboxine B_2, and the
13 results with Ibuprofen reflect what happened with
14 aggregation, very clear and marked inhibition of serum
15 Thromboxine B_2 at a therapeutic dose of Ibuprofen, but
16 a rather mixed picture here with little or no
17 significant inhibition of serum Thromboxine B_2. As
18 you can see, there is some bouncing around here, but
19 no dose-dependent inhibition. Nevertheless, with the
20 bouncing in a single dose administration like this, it
21 was clear we needed to do longer dosing to achieve
22 steady state and get a better idea of the activity of
23 the compound.
24 This was done in this study where we
25 administered Celecoxib at 200 or 400 mg twice a day

1 and compared it to Naproxen at its full therapeutic
2 dose. It is evident that Naproxen is a very potent
3 inhibitor of Thromboxine production in platelets in
4 this particular model, whereas at 200 and 400 mg,
5 Celecoxib had absolutely no effect on serum
6 Thromboxine. Now you will see later on in Dr. Geis's
7 presentation that the maximal therapeutic dose where
8 we achieve maximal efficacy in rheumatoid arthritis is
9 200 mg twice a day. So this means that at 400 mg,
10 twice the maximum therapeutic dose, we have no effect.
11 So a clear therapeutic margin there.
12 We can also look at the ability of
13 Celecoxib to work on COX-2 under similar kinds of
14 conditions. Now in this case, we can add directly the
15 compound to a test tube and know exactly how much is
16 there. Measuring platelets, as I just mentioned, or
17 we can measure COX-2 within this petrono assay, where
18 we measure prostaglandin formation from activated
19 monocytes. In this example of one subject's blood, we
20 measure then the addition -- or we add various
21 concentrations of Celecoxib and see concentration-
22 dependent potent inhibition of COX-2, and again a
23 clear separation in COX-1.
24 Well, how does that translate into what
25 blood levels we might achieve therapeutically? Again,

1 I will precede a bit what you will see from Dr. Geis
2 and say that 100 or 200 mg bid are the doses we will
3 be using, and the plasma levels that we achieved, the
4 range, is shown here. Again, this would suggest then
5 that this plasma range is capable of fully inhibiting
6 COX-2.
7 So this translates then into this
8 conclusion, which is that at twice the maximum
9 therapeutic dose, Celecoxib causes no effect on
10 platelet aggregation, no effect on Thromboxine
11 production, and therefore is COX-1 sparing, and it
12 contrasts clearly with all of the non-steroidals which
13 have marked effects here at therapeutic doses.
14 Well, along the way we assessed very
15 carefully the selectivity and specificity of Celecoxib
16 in in-vivo assays. I won't show you that data today,
17 but rather move on to the anti-inflammatory and
18 analgesic activity. Over the course of the past six
19 years, it is clear there is very much evidence that
20 suggests that COX-2 is important in both inflammation
21 and pain. I will show you two or three examples of
22 the activity of Celecoxib in such assays.
23 There are acute and chronic models of
24 inflammation that have been widely used over the past
25 three decades. In this model, acute inflammation is

1 initiated and we have measured the effect or monitored
2 the effect of Celecoxib compared to Naproxen, both at
3 their maximum doses. And what we see is that Celecoxib
4 is capable of reducing or preventing inflammation to
5 the same extent as a maximum dose of Naproxen. Now
6 neither can completely reduce inflammation in this
7 model because it is due to other mediators, bradykinin
8 and so forth.
9 Well, what is the biochemical mechanism by
10 which these work? That is illustrated on the right-
11 hand panel, where we have measured prostaglandin
12 formation at the inflammatory site. The picture is as
13 shown. There are basal levels of prostaglandin that
14 we can find. In fact, you can find basal levels of
15 prostaglandin in most every tissue, but in the
16 inflamed tissue we see a clear elevation above that,
17 a marked increase in prostaglandin formation.
18 Celecoxib has no effect on those basal levels of
19 prostaglandin. By contrast, though, it prevents the
20 increase in prostaglandins that is caused by
21 inflammation.
22 Now in stark contrast, Naproxen inhibits
23 both the basal levels of prostaglandin but also the
24 inflamed. Now this suggests a clear hypothesis or
25 interpretation, which I show here. Again, this is our

1 hypothesis that the basal levels of prostaglandins are
2 produced by COX-1 and they have no contribution to
3 inflammation or pain. These elevated levels
4 associated with inflammation are, in fact, derived
5 from COX-2, and those are the prostaglandins that
6 contribute to inflammation, and as I will show you in
7 a moment, pain.
8 Well, this is the hypothesis, and I will
9 show you one of the ways that we tested that
10 hypothesis, and that was using a pharmacological
11 reagent SC-560 shown on the left. This compound is
12 very similar structurally to Celecoxib, but it lacks
13 the key feature that allows for specificity. In fact,
14 it shows the opposite profile. It is a very potent
15 inhibitor of COX-1, but has again a clear two to three
16 order of magnitude separation in its activity on COX-
17 2. So with this sort of profile of a very highly
18 specific COX-1 inhibitor, we could go in and ask what
19 is the activity of a specific COX-1 inhibitor in this
20 same model.
21 We first assessed the oral bioavailability
22 of 560, looking at its effect on COX-1 related
23 prostaglandins from the GI tract or inflammatory
24 prostaglandins from COX-2. We see very potent
25 inhibition, again after oral administration of gastric

1 prostaglandin, suggesting that this was then an
2 appropriate tool for the analysis. And what we found
3 is shown here. Inflammation was induced, reduced to
4 the same effect level here with Celecoxib that is
5 achieved with maximal doses of nonsteroidals, and very
6 clearly no effect of 560 on either inflammation or in
7 this case we also measured pain response in the same
8 model.
9 A further suggestion that COX-1 is not
10 important in pain is shown in this experiment where we
11 compared Ketorolac, a very potent mixed inhibitor of
12 COX-1 and COX-2 to Celecoxib. And in this case, we
13 allowed the pain response to become maximum and then
14 dosed with either drug. What we see is a rapid
15 diminution of the hyperalgesia by Ketorolac and a
16 similar diminution of hyperalgesia by Celecoxib,
17 suggesting that even once the pain state has reached
18 its maximum, it is still dependent totally on COX-2
19 and COX-1 has no influence.
20 We have also evaluated Celecoxib in a
21 number of chronic modules. I will show you the rat
22 adjuvant arthritis model, which is characterized by
23 very vigorous inflammation and joint destruction. And
24 in this model, we find that therapeutic dosing with
25 Celecoxib causes a prompt reversal of the

1 inflammation. Importantly, the reversal of
2 inflammation is equivalent at a maximum dose to what
3 is achieved with a maximum dose of Indomethacin, a
4 very potent mixed inhibitor of COX-1 and COX-2,
5 suggesting again in this model as well that COX-2 is
6 actually the important isoform.
7 Dose response analysis in this same model
8 is shown here. And from this dose response, we could
9 estimate the plasma levels that would be necessary to
10 achieve a therapeutic benefit. I use these actually
11 to suggest doses for the clinical, and as it turns
12 out, the dose here of .8 micromolar is approximately
13 the C-max we see at 100 mg bid, suggesting a good
14 concordance between these models and what is seen
15 clinically.
16 Well, the totality of this data would then
17 suggest that COX-2 in fact is the therapeutic target
18 of the nonsteroidals.
19 The profile that I have shown you so far
20 of Celecoxib suggested then that it was appropriate to
21 carry forward into further development and safety
22 analysis. It went through the usual battery of safety
23 studies, both acute and chronic. In these studies, we
24 used rats and dogs, and we have safety up to two years
25 in rats and up to one year in dog. It is important to

1 emphasize at this point that we were actually able to
2 carry forward safety studies in dogs. Nonsteroidals
3 are not -- you cannot do this kind of an analysis.
4 because the dogs are very sensitive to the
5 nonsteroidals and will die of GI injury before you
6 could ever achieve a therapeutic dosing for one year.
7 And it is important to note that we were able to
8 achieve, again, exposures well above the therapeutic,
9 and we did not see any toxicity that was unusual. So
10 at high -- relatively -- what we would consider high
11 level inhibition of COX-2 in the dog and in the rat,
12 we saw nothing that was new.
13 Well, as the program went along, we of
14 course became aware that COX-2 was not -- the model
15 that we showed originally was quite a bit simplified.
16 And there in fact is COX-2 present in a number of
17 different tissues, constitutively or induced by
18 physiological stimuli, for example in the female
19 reproductive tract. It is also present in the kidney
20 and the brain. We looked in our safety studies
21 particularly at these areas for particular attention.
22 I will spend -- as well as on the tissues where COX-1
23 is present.
24 In pregnancy and female reproduction then,
25 we saw no effect on ovulation or fertility and no

1 effect whatsoever on male fertility either. We did
2 see some effects on embryo viability -- this is
3 implantation. Again, only at exposures which were
4 very much above those needed for therapeutic benefit.
5 Now as expected, we did not see any
6 effects on bleeding based on the COX-1 related effects
7 there. And importantly, in the CNS we saw no
8 structural changes, and in the behaviors that we could
9 monitor in these kind of safety studies, we did not
10 see any CNS effect. So there was nothing there that
11 we saw that caused a concern. In the kidney, we did
12 not observe renal capillary necrosis. Now RPN in the
13 rat is a common sequelae of dosing with a mixed COX-
14 1/COX-2 inhibitor. And that was not observed in the
15 rat, suggesting that that is a COX-1 mediated effect.
16 We did see transient anti-natriuresis in rats, and
17 that was echoed in the clinical findings in the humans
18 you will see from Dr. Geis.
19 Finally, the toxicity that we could have
20 eventually observed if we dosed high enough -- again,
21 we could surmount the selectivity and we would
22 eventually see some GI effects in both rats and dogs.
23 To summarize, based on these preclinical
24 findings, it appears that Celecoxib then -- this
25 mechanism-based approach to drug targeting is

1 delivered within an agent which specifically binds to
2 COX-2, and it has the efficacy of the NSAIDS in
3 arthritis and pain, at maximal efficacy. But by
4 sparing then the COX-1 -- not affecting COX-1 -- we
5 achieved the specificity. And I would like to
6 emphasize then that what we have done compared to the
7 nonsteroidals is simply remove the left-hand part of
8 this. We are not adding on any extra inhibition that
9 would not have been observed in clinical practice with
10 the non-steroidals, which in fact are COX-2
11 inhibitors. Therefore, our safety studies support
12 that as well that no unusual toxicities are apparent
13 with this inhibition of COX-2 alone, and that
14 therefore this gives us what we think, based on the
15 preclinical, is a specific COX-2 inhibitor. Now this
16 all has to be demonstrated in the clinic, and you will
17 see the human evaluation of that from Dr. Geis. Thank
18 you.
19 CHAIRMAN ABRAMSON: Any questions for Dr.
20 Isakson?
21 DR. MCCARTHY: Denis McCarthy,
22 Albuquerque. Could you give us an idea about the
23 range of plasma concentrations that you see following
24 oral dosage? I presume that the shaded area that you
25 showed were mean concentrations at the steady state or

1 something like that.

2 DR. ISAKSON: Yes. That is actually human

3 clinical data, and I think I would probably like to

4 defer that to Dr. Karim, who will actually address

5 that very elegantly in just a moment.

6 DR. MCCARTHY: Thank you.

7 CHAIRMAN ABRAMSON: Okay. Thank you.

8 DR. KARIM: Good morning. Celecoxib

9 pharmacokinetic has been evaluated extensively in more

10 than 1,500 subjects in 32 different clinical studies.

11 These studies can be divided into five major

12 categories. Studies involved to investigate the basic

13 pharmacokinetic profile of Celecoxib, pharmacokinetic

14 Celecoxib in special populations, drug/drug

15 interaction studies, population pharmacokinetic

16 dynamic analysis of pivotal clinical trial data, and

17 bioequivilency establishment of clinical trial batches

18 and commercial formulation.

19 Celecoxib is a low solubility, high

20 permeability drug which is rapidly and extensively

21 absorbed. It lacks the asymmetric center as an

22 achiral mixture, so it doesn't have the complexity or

23 the enantiomer mixture pharmacokinetics as is obtained

24 in many of the currently available NSAIDS. It

25 undergoes extensively metabolism, and less than 3

1 percent of the dose is excreted either in the urine or
2 feces. The primary and the most important pathway in
3 the metabolism of Celecoxib is hydroxilation of this
4 methyl group to give you this primary alcohol.
5 Through a variety of in-vitro and in-vivo techniques,
6 we have actually identified the cytochrome P450 2C9 a
7 the major cytochrome involved in this
8 biotransformation pathway. Identification of this
9 isozyme is very important because it allows us a
10 rational method of selecting other drugs for carrying
11 out drug/drug interaction studies.
12 This alcohol metabolite, which apparently
13 is inactive, is seen in the plasma but not in the
14 urine or feces because it undergoes further metabolism
15 to this carboxylic acid. About 18 percent of this
16 carboxylic acid is excreted in the urine and about 54
17 percent in the feces. The total recovery of this
18 carboxylic acid, which is also an inactive metabolite,
19 is 73 percent. Now if you assume that this carboxylic
20 acid is formed in the liver and its presence in the
21 feces is due to the biliary excretion, then you can
22 estimate that as much as 73 percent of the dose was
23 absorbed. A very minor amount of this carboxylic acid
24 is further converted to glucuronidide conjugate.
25 The next slide shows a typical plasma

1 concentration time curve of Celecoxib following
2 administration of the drug on an empty stomach shown
3 in the red line here and immediately after a high fat
4 breakfast. Following drug dosing with meals, there is
5 a very small lag period followed by an increase in
6 bioavailability. The increased bioavailibility is
7 around 10 or 20 percent. And for a drug like
8 Celecoxib, which has a very wide therapeutic window,
9 this increase is not clinically important.
10 We are recommending that for chronic
11 administration, Celecoxib can be given with or without
12 food. When given on an empty stomach, a 200 mg single
13 dose of the drug gives you a peak level of around 700
14 ng/ml, and the percent standard deviation is around 40
15 to 50 percent. T-max occurs around two to three
16 hours. The clearance of the drug is 30 liters per
17 hour. The volume of distribution is 400 liters, which
18 indicates very extensive tissue distribution of the
19 drug. The effective half-life is around 11 hours.
20 One interesting point is that at 24 hours, we do see
21 detectable plasma levels of Celecoxib following drug
22 dosing with meals or under fasting conditions, which
23 suggested once a day dosing is possible.
24 I would now like to discuss the
25 pharmacokinetics of Celecoxib in special populations.

1 First, we have examined the trough concentration in
2 osteo and rheumatoid arthritis patients, and we have
3 found no difference in pharmacokinetics in this
4 patient group. Also, the pharmacokinetics in non-
5 Insulin diabetic patients is also similar to a normal
6 subject. In chronic renal failure, the clearance of
7 the drug is in fact slightly increased. The next two
8 slides will show the effect of age, gender, weight and
9 race on pharmacokinetics of Celecoxib as well as
10 effect of hepatic impairment.
11 This graph shows the relationship between
12 steady state clearance adjusted for 70 kg body weight
13 versus the age. The age group ranges anywhere from 20
14 years right up to 85 years. There is a very weak
15 correlation, as you can see, that increased age
16 results in a slight decrease in clearance. If you
17 really look at the regression line, you can estimate
18 that someone 30 years of age would have an average
19 clearance of 32 liters per hour, which would be
20 decreased to only 22 liters per hour for someone 80
21 years old. This 31 percent decrease in clearance is
22 really not clinically important for a drug like
23 Celecoxib.
24 Now half of the subjects here were female
25 and half were male. So we did an analysis of variance

1 to see if there is a gender effect in clearance, and
2 there was no gender effect in clearance. 13 of the
3 subjects here were of African American origin, and we
4 found that African Americans had 30 to 40 percent
5 lower clearance. Again, this magnitude of change in
6 clearance is not clinically important. There is one
7 subject here who was clearly an outlier, and
8 genotyping studies in this subject showed that this
9 subject was a poor metaboliser of P450 2C9.
10 This particular figure shows the plasma
11 concentration of Celecoxib in hepatic impaired
12 patients. Hepatic impairment was classified according
13 to the Charles Spew severity index, classification A
14 and classification B.
15 CHAIRMAN ABRAMSON: Excuse me, Dr. Karim,
16 I am sorry to interrupt you, but could you convert
17 ng/ml to micromolar, which is how it was presented by
18 Dr. Isakson? Could you give us a range there?
19 DR. KARIM: Yes. 300 ng/ml -- Peter, what
20 was your micromolar? The molecular weight is 381.
21 DR. ISAKSON: Yes. 600 would be 1.6
22 micromolar.
23 CHAIRMAN ABRAMSON: Okay. Thank you.
24 Sorry.
25 DR. KARIM: The left panel shows the

1 plasma levels in normal subjects and patients with
2 hepatic impairment, and there was no significant
3 difference in the area under the curve for one-dose
4 interval. Since Celecoxib is metabolized extensively
5 and the elimination pathway is due to hepatic
6 metabolism, we were expecting the plasma level to be
7 higher in patients with moderate hepatic impairment,
8 and there was an increase in the plasma level in
9 moderately hepatic impaired patients. We have not
10 studied Celecoxib pharmacokinetics in patients with
11 severe hepatic impairment.
12 Now in our data base of pharmacokinetic
13 information available, either sparse or intense, 1,566
14 subjects, we have identified 6 subjects in whom plasma
15 levels are unusually high. These are the subject
16 numbers, the study numbers, age, weight, sex, race,
17 dose. AUC(tau) indicates AUC during one dose
18 interval, 0 to 12 hour, clearance and C-max. None of
19 these subjects showed adverse experience. Subject 12
20 and subject 31 were in fact the same subject who
21 participated in two different studies. We do not have
22 AUC data for these two subjects, 827 and 461, because
23 they had only one or two plasma samples. They
24 participated in population pharmacokinetic studies.
25 The highest exposure we have seen to date in our

1 clinical development of Celecoxib is in subject 12.
2 Subject 12 received 600 mg bid of Celecoxib in a high
3 dose platelet effect study. And if you look at the
4 AUC, it is 166 mcg/ml times hour. A normal
5 therapeutic range would be only 7 mcg/ml times hour.
6 The peak level in this subject was 16.3 mcg/ml, where
7 therapeutic levels are only around .3 mcg/ml. This
8 subject participated in the high dose platelet effect
9 study, so we had both pharmacokinetic and dynamic data
10 available on this subject. Here are the results of
11 percent platelet aggregation response to arachidonic
12 acid with placebo treatment and subject 12. You can
13 see that despite the very high exposure, the platelet
14 aggregation data were almost identical to placebo. In
15 the same study, we had Ibuprofen. You can see the
16 normal therapeutic dose of Ibuprofen had a marked
17 pharmacodynamic response on platelet aggregation.
18 In my last two slides now, I will review
19 for you the drug/drug interaction studies. The
20 drug/drug interaction pharmacologic basis for
21 drug/drug interaction were NSAIDS are known to
22 decrease the renal blood flow, and thus they have a
23 potential to decrease the renal clearance of the drugs
24 which are exclusively excreted by the kidney and they
25 have a narrow therapeutic window. These two drugs are

1 Methotrexate and Lithium. We therefore examined the
2 effect of Celecoxib on the renal clearance of
3 Methotrexate and Lithium. NSAIDS are known to be also
4 metabolized by 2C9, and they have a potential to
5 interact with other drugs which are also substrates
6 for 2C9. We, therefore, examined the effect of
7 Celecoxib on the metabolism and clearance of Warfarin,
8 Tolbutamide and Phenytoin. NSAIDS are also highly
9 bound to plasma protein, and they may have a potential
10 for protein binding displacement interaction, so we
11 also examined the effect of Celecoxib on plasma level
12 and dynamics of Glyburide.
13 The two most important interactions
14 therapeutically are Methotrexate and Warfarin. In the
15 case of Methotrexate, we had patients who were already
16 established on their usual dose of Methotrexate. We
17 measured the plasma level of Methotrexate when they
18 started the study and after a one-week treatment with
19 placebo. And as you can see, as expected with
20 placebo, the plasma level did not change at all. This
21 subject then received Celecoxib 200 mg bid and
22 Celecoxib treatment had no influence on the plasma
23 level of Methotrexate. There was no statistically
24 significant difference either in C-max or AUC.
25 For Warfarin interaction study, we had 24

1 subjects divided into two groups of 12 subjects each.
2 The subjects received a loading dose of Warfarin
3 followed by a maintenance dose. On day 7, their
4 maintenance dose was given with placebo. You can see
5 that the prothrombin time remained constant with
6 placebo all the way. In group B subjects, they
7 received the usual loading dose followed by a
8 maintenance dose, but here the Warfarin was
9 administered together with Celecoxib 200 mg bid, and
10 you can see that administration of Celecoxib with
11 Warfarin resulted in no change in prothrombin time.
12 In summary then, Celecoxib is a low
13 solubility, high permeability drug with a systemic
14 availability of at least 73 percent. It has a
15 clearance of 30 liters per hour, a distribution volume
16 of 400 liters, a half-life of 11 hours. It is
17 extensively metabolized to inactive compound via P450
18 2C9. Its protein binding is 97 percent and
19 concentration independent. There is an advantage for
20 giving Celecoxib with or without food, and there is a
21 potential for once-a-day dosing. There is a lower
22 clearance -- that is, higher AUC in elderly women.
23 This is partly attributed to lower body weight and
24 partly to age. But the magnitude of the difference is
25 not high enough and not clinically important. There

1 is also high exposure and high AUC in moderately
2 hepatically impaired patients. We have not studied
3 severely hepatically impaired patients. And a slight
4 change in clearance in African Americans, again not of
5 clinical significance. Lastly, there is no drug/drug
6 interaction of clinical significance with
7 Methotrexate, Lithium, Warfarin, Phenytoin, Glyburide
8 and Tolbutamide. That was my last slide. Dr. Geis
9 will now talk about the safety and efficacy of
10 Celecoxib. But if there are any questions, I will be
11 happy to answer them.
12 CHAIRMAN ABRAMSON: I just have one
13 question. Trying to relate the clearance data to
14 plasma levels and what the consequences may be. Even
15 at individual ages -- at age 30, there were wide
16 variations in clearance from 10 to 80. I am curious
17 as to how that might translate into the plasma levels.
18 DR. KARIM: Well, to us
19 pharmacokineticists, one of the most important
20 parameters is the clearance. But the clearance
21 decrease has to be looked upon in terms of the
22 therapeutic window of the drug. Now a clearance of 40
23 to 50 percent for a drug with a narrow therapeutic
24 window like Warfarin might be important. But for
25 Celecoxib, it is such a wide therapeutic window that

1 a clearance of 30 to 40 percent change really has no
2 clinical importance. And you are absolutely right,
3 there is a wide variability in the clearance of the
4 drug.
5 DR. MCCARTHY: Could you give us an
6 average plasma concentration at the steady state in
7 micromoles for the 100 bid and 200 bid doses in
8 ordinary subjects, not in the outliers?
9 DR. KARIM: Yes. In ordinary subjects,
10 the peak level after 200 mg bid would be about 1
11 mcg/ml, 1000 ng/ml. The molecular weight is 381. You
12 will have to do the ratio. And with 100 mg bid, you
13 will have half that level. Those are peak levels.
14 The trough level would be about one-third of those.
15 CHAIRMAN ABRAMSON: Okay. Any other
16 questions? Thank you very much.
17 DR. KARIM: Dr. Geis?
18 DR. GEIS: Our working hypothesis has been
19 that specific inhibitors of COX-2 will be anti-
20 inflammatory and analgesic, but without the typical
21 side effects of NSAIDS. Preclinical data have shown
22 that Celecoxib is a specific COX-2 inhibitor.
23 Clinical studies were conducted to confirm this in
24 humans.
25 The objectives of the clinical program

1 were to demonstrate the efficacy of Celecoxib in
2 treating the signs and symptoms of osteoarthritis and
3 rheumatoid arthritis, and also to demonstrate the
4 efficacy of Celecoxib in the management of pain. In
5 addition, we collected data and conducted specific
6 clinical trials to differentiate Celecoxib from NSAIDS
7 in terms of its GI effects, its effects on platelets,
8 and its overall general safety.
9 Our program has been very extensive and
10 was predominantly conducted in the United States and
11 Canada. There were 51 studies and over 13,000 study
12 participants. In our GI program, we conducted or
13 performed close to 5,000 or close to 5,000 patients
14 underwent endoscopy. At the time we submitted the
15 NDA, there was about 1,000 patients who had been
16 exposed to Celecoxib for one or more years, and this
17 equated to about 3,000 patient years of exposure.
18 We recently completed a safety update, and
19 at that time there were about 2,000 patients who had
20 received the compound for one or more years, and that
21 equated to about 5,000 patient years of exposure.
22 I would now like to move into the clinical
23 trials demonstrating the efficacy of Celecoxib in
24 treating osteoarthritis. We performed five pivotal
25 trials. Three were 12 weeks in duration and two were

1 6 weeks in duration. The 12-week studies included two
2 trials conducted in patients with osteoarthritis of
3 the knee and one study in patients with osteoarthritis
4 of the hip. Both the 6-week studies were conducted in
5 patients with osteoarthritis of the knee.
6 Patients were eligible for study
7 participation if they had osteoarthritis and were
8 taking an NSAID. The NSAID was discontinued and the
9 patient's condition exacerbated. When the patient
10 reached predefined criteria for a flare, they were
11 then eligible to be randomized to one of five
12 treatment groups. Treatments included placebo,
13 Naproxen, and one of three doses of Celecoxib. We
14 chose Naproxen as the active comparator since it is
15 the most commonly prescribed NSAID in the U.S., since
16 its half-life is very similar to Celecoxib, and since
17 it is considered a powerful anti-inflammatory and
18 analgesic.
19 The doses of Celecoxib in these studies --
20 50 mg bid, 100 mg bid, or 200 mg bid -- were based on
21 preclinical data, human pharmacokinetic data, and the
22 results of our phase II clinical trials. Once
23 enrolled into the study, the patients underwent
24 arthritis assessments at baseline and then
25 periodically for the 12 weeks of study participation.

1 This slide shows some of the measures of
2 OA efficacy that were collected in these studies. The
3 included the patient's assessment of pain using the
4 visual analog scale, the WOMAC OA index with subscales
5 for pain, function and stiffness, patients' and
6 physicians' global assessments of their arthritis, and
7 to assess health-related quality of life, we used the
8 SF-36 health survey. In each of these trials,
9 approximately 200 patients were enrolled per treatment
10 group, for approximately 1,000 patients per study and
11 approximately 3,200 patients who participated in these
12 three pivotal OA studies. Baseline demographics for
13 the patients are described in your briefing document.
14 All the measures of efficacy yielded
15 similar results, and today I would like to show you
16 some data that is representative of all the results we
17 obtained. Here we show the pool data of patients'
18 disposition in these studies. Approximately 40
19 percent of placebo patients completed the study,
20 whereas about 60 percent of patients in the active
21 treatment groups completed the studies. The early
22 withdrawals in the placebo group were predominantly
23 due to treatment failure, and this was much lower in
24 the active treatments. Early withdrawals due to
25 adverse events and for other reasons such as protocol

1 noncompliance were very low and similar across the
2 treatment groups.
3 This slide shows the patients' assessment
4 of pain using the visual analog scale for one of the
5 OA trials in patients with OA of the knee. As seen at
6 baseline, patients in all the treatment groups began
7 with scores of about 70 mm, indicating moderate to
8 severe pain. There was a placebo response. However,
9 the responses to Celecoxib at the two higher doses and
10 Naproxen were statistically superior to placebo at all
11 time points. There were no statistical differences
12 between the high doses of Celecoxib and Naproxen. The
13 results shown here were replicated in the second trial
14 in patients with OA of the knee and then in the third
15 trial in patients with OA of the hip.
16 Another measure of efficacy that I would
17 like to show you today which confirms what we see here
18 is the patients' WOMAC subscale for physical function.
19 Here we show the results from the three trials, and as
20 seen there is a modest placebo response, but the
21 responses to Celecoxib at the two higher doses and
22 with Naproxen were statistically superior to placebo
23 at all time points and replicated in all trials. The
24 50 mg dose did not routinely and consistently show
25 superiority to placebo for all our measures of

1 efficacy.

2 Now here we show the SF-36 health survey

3 results for the physical health domain from our hip OA

4 pivotal trial. And as you can see, there was

5 improvement in the patient's health-related quality of

6 life with the two higher doses of Celecoxib and

7 Naproxen, and these differences compared to placebo

8 were statistically significant. And the results shown

9 here are representative of what was seen in the other

10 OA trials.

11 Now based on our preclinical data and our

12 pharmacokinetic data in humans, there was the

13 possibility or the data suggested the possibility that

14 Celecoxib administered once per day would be

15 efficacious. We tested this hypothesis by conducting

16 two pivotal OA trials of six weeks in duration. This

17 trial involved patients with osteoarthritis whose

18 NSAID was removed and the patients went into a flare

19 state. In this study, patients were randomized to

20 receive either placebo, Celecoxib 100 mg twice a day,

21 or Celecoxib 200 mg once a day. Arthritis assessments

22 were performed at baseline, at week two, and week six.

23 These trials involved approximately 200

24 patients per treatment group, for a total of about

25 1,400 patients who participated in these studies.

1 Here we show the pooled data of patients' disposition
2 in the two studies with a higher percentage of
3 patients in the two Celecoxib groups completing the
4 study compared to placebo, and again placebos commonly
5 withdrew early due to treatment failures.
6 Here we show the patients' assessment of
7 pain as measured on a visual analog scale from the two
8 studies. The results are remarkably similar to what
9 we saw with the 12-week studies. In both trials,
10 patients started the study with about 70 mm of pain.
11 There was a modest placebo response, but the responses
12 to Celecoxib at both dose regimens were statistically
13 superior to placebo in these replicate studies. The
14 responses to Celecoxib once a day and twice a day were
15 virtually identical and were not statistically
16 significant from one another. This was confirmed by
17 the other measures of efficacy in these particular
18 studies, and here we show the WOMAC physical function
19 at week six, showing improvement in physical function
20 at both dose regimens of Celecoxib compared to placebo
21 and again replicated in the trials.
22 The conclusions of our OA program are
23 shown here. The data indicates that Celecoxib is
24 efficacious in treating osteoarthritis. The
25 recommended dose is 200 mg per day. The data indicate

1 that the dose can be administered as a single dose or
2 divided doses. And the efficacy of Celecoxib is
3 similar to Naproxen.
4 I would now like to move into our
5 rheumatoid arthritis program. We conducted two 12-
6 week pivotal trials that were identical. Candidates
7 for study participation were patients with rheumatoid
8 arthritis who were taking NSAIDS to control the signs
9 and symptoms of the arthritis. The NSAIDS were
10 withdrawn and the patients' condition exacerbated, and
11 they must have reached predefined criteria of a flare
12 before being randomized into the trial. The patients
13 received either placebo, Naproxen or Celecoxib at 100
14 mg twice a day, 200 mg twice a day, or 400 mg twice a
15 day. Arthritis assessments were performed at baseline
16 and then periodically for the 12 weeks of these
17 studies.
18 Here are some of the measures of RA
19 efficacy that were collected. They included the ACR-
20 20 responder index, the number of swollen joints, the
21 number of tender and painful joints, physicians' and
22 patients' global assessments of arthritis, and then to
23 assess health-related quality of life, we collected
24 information on the SF-36 health survey.
25 As with the previous studies described, we

1 enrolled approximately 200 patients per treatment
2 group per study, for a total in this portion of the
3 program of approximately 2,200 patients. And again,
4 baseline demographics are described in your briefing
5 document, and the demographics were similar across
6 treatment groups in all the studies.
7 Here we show the pooled data of patients'
8 disposition in the two RA trials. And very similar to
9 what we saw in the OA trials, with the percent of
10 patients in the placebo group who completed the
11 studies was about 40 percent, with about 60 percent
12 completing study participation in the active treatment
13 groups. Again, the most common reason for early
14 withdrawal with placebo was due to treatment failure.
15 Here we show the ACR responder index for
16 one of the two studies. As seen in the placebo group,
17 about 30 percent of the patients were considered
18 responders by ACR criteria compared with approximately
19 40 percent in the active treatment group. And this was
20 statistically different from placebo. There was no
21 difference across the active treatment groups. And
22 these data were repeated in the second RA trial.
23 Here we show the number of swollen joints
24 from the two studies. We examined 66 joints in each
25 patient at the beginning of the studies. The patients

1 entered with about 22 swollen joints in each trial.
2 There was a reduction in the number of swollen groups
3 in the placebo group in both studies, but there was a
4 greater reduction which was statistically different
5 from placebo with all active treatments. There was no
6 difference across the active treatment groups in the
7 reduction and number of swollen joints in the two
8 trials.
9 Again, we show the SF-36 physical health
10 domain from one of the studies, but it is
11 representative of both. And as seen here, all doses
12 of Celecoxib were superior to placebo in improving
13 health-related quality of life as measured by these
14 health domains.
15 To determine the durability of Celecoxib,
16 we conducted a six-month rheumatoid arthritis trial.
17 In this trial, patients who had rheumatoid arthritis
18 who were symptomatic were eligible for study
19 participation. These patients did not have to undergo
20 a flare. They simply had to have some symptoms of
21 their rheumatoid arthritis. They were randomized to
22 receive Celecoxib at 200 mg twice a day or Diclofenac
23 SR 75 mg twice a day. Arthritis assessments, again,
24 were performed periodically during the study and in
25 the study of six months duration.

1 We show here the number of tender and
2 painful joints in the patients and the number of
3 swollen joints. As seen, the number of symptomatic
4 joints decreased during study participation in both
5 treatment groups. Typically, there was not a
6 statistically significant difference between the
7 treatment groups. However, at one point at week 16,
8 the reduction in tender painful joints was greater
9 with Celecoxib than it was with Diclofenac. Of note,
10 the response to both treatments was maintained
11 throughout the entire duration of the trial.
12 And here we show the conclusions from our
13 rheumatoid arthritis program. The data indicate that
14 Celecoxib is efficacious in treating the signs and
15 symptoms of rheumatoid arthritis. The recommended
16 dose is 100 mg twice a day, but some patients may
17 benefit by increasing the dose to a maximum of 200 mg
18 twice a day. Efficacy was similar to Naproxen and
19 efficacy was sustained with chronic therapy.
20 I would now like to move into our
21 management of pain program. As shown in the previous
22 study, Celecoxib was efficacious for treating the pain
23 of chronic arthritis or the chronic pain of arthritis.
24 We then conducted trials to assess the efficacy of
25 Celecoxib for acute pain and then short-term pain.

1 We used two models of pain. The first
2 model, which was the acute pain model, was a post-
3 surgical model. We conducted three pivotal studies
4 using post-dental surgery, and these studies looked at
5 the efficacy of a single dose of Celecoxib. We then
6 conducted a single post-orthopedic surgery study which
7 was considered to be a supporting trial and also it
8 involved a repeat dose of Celecoxib.
9 Our second pain model, and that is a model
10 for short-term pain from one to seven days in
11 duration, was the OA flare model. We conducted three
12 pivotal studies with this model and this was a
13 multiple dose model. This slide shows the design of
14 the post-dental surgery studies. Study participants
15 were patients who had one or more third molars removed
16 of which one must have been mandibular and required
17 bone removal. After anesthesia had worn off and the
18 patients had reached moderate to severe pain, they
19 were randomized to receive either Celecoxib, an NSAID
20 formulation or placebo. Across these three studies,
21 we tested doses of Celecoxib ranging from 25 mg up
22 through as high as 400 mg. After the single dose of
23 the study medication, pain assessments were collected
24 at various time points during the observation period.
25 Measures of efficacy in this model

1 included time to onset of pain relief, time specific
2 pain relief, as well as the duration of pain relief.
3 Each of these studies included about 50 patients per
4 treatment group. The NSAID formulations that were
5 used included Ibuprofen 400 mg and Naproxen Sodium 550
6 mg. We used NSAID formulations as the active
7 comparators to validate each specific study. The
8 choice of these particular active comparators was in
9 conjunction with discussions with the FDA.
10 Although we conducted or we used a variety
11 of doses of Celecoxib, I would like to focus on the
12 results from the 100 and 200 mg patients. Now here we
13 show time specific pain relief in the three trials.
14 An increase in the mean score indicates greater pain
15 relief. What we show by the bars at the top of each
16 graph are the time points at which the particular
17 active comparator was statistically superior to
18 placebo. And as we can see, Celecoxib at 200 mg and
19 100 mg was statistically superior to placebo in terms
20 of pain relief beginning at or before one hour and
21 continuing through the 12-hour observation period.
22 This was also seen with the NSAID formulation active
23 comparators. In addition, the NSAID formulations were
24 statistically superior to Celecoxib, but only during
25 the first few hours after the single dose.

1 Now the next slide will show the sum of
2 the time-specific pain relief scores over the entire
3 12-hour period as sort of an assessment of the
4 integrated pain response for these patients with time.
5 And here we show the sum of these time specific pain
6 relief score called the TOTPAR, and as seen, Celecoxib
7 100 and 200 mg was statistically superior to placebo
8 as were the active NSAID formulations.
9 I would now like to describe our
10 supporting study using the post-orthopedic surgery
11 model. Patients who were candidates for this study
12 had undergone an orthopedic procedure, and after
13 anesthesia had worn off and they had achieved moderate
14 to severe pain, they were randomized to receive
15 placebo, Darvocet N-100 qid, or Celecoxib at doses of
16 100 mg or 200 mg bid. Now these were prn dosings, and
17 I will show you the dosing schedule on the next slide.
18 The patients were followed for 24 hours
19 after dosing and pain assessments were collected. So
20 in this study, all patients received their first dose
21 and then were allowed a second dose. But the second
22 dose was administered only at or greater than 4 hours
23 after the first dose. So the Celecoxib-treated
24 patients received their second dose only at 4 hours or
25 greater than after the first dose as did the Darvocet

1 patients. Celecoxib patients again only received two
2 doses, where Darvocet patients were allowed to receive
3 all four doses.
4 Now the next slide shows the time specific
5 pain relief after patients were administered their
6 dosing. And as we see here, there was a very dramatic
7 placebo response in the first few hours which then
8 tapered off. As shown here, Celecoxib at 100 and 200
9 mg as well as Darvocet was statistically superior to
10 placebo at quite a bit of the time after the exposure
11 to the drug or after dosing.
12 I would now like to move on to our second
13 model of pain, which is short-term pain, using the OA
14 flare model. This slide shows our rationale for using
15 this model as a -- or using OA flare as a model of
16 pain. Pain is the primary symptom of OA. Non-anti-
17 inflammatory agents such as Tylenol and opiates are
18 efficacious in treating OA pain and also the OA model
19 has been used to evaluate the efficacy of a variety of
20 analgesics including opiates and central-acting
21 analgesics.
22 Now the OA flare data was part of our
23 three pivotal 12-week OA studies, and this was
24 identified as an objective in these trials. So the
25 patients in the pivotal trials, once they underwent

1 the flare and once they were randomized to one of the
2 treatments, were then asked to answer questions about
3 their OA pain on a daily basis using the APS pain
4 measures for the first seven days. This slide shows
5 the questions in the APS pain measure questionnaire.
6 There were five questions and they ranged from
7 questions such as have you experienced any pain in the
8 last 24 hours to a question about what was your worst
9 pain as well as what was your average pain. Each
10 question was scored separately and analyzed
11 separately. This slide shows the data in terms of
12 average pain in the past 24 hours for one of the three
13 trials. The score range was 0 to 10 and patients
14 entered with mean scores of about 6.5
15 As seen, there was a placebo response or
16 a reduction in pain, but also with Celecoxib at 100
17 and 200 mg twice a day, the response was greater and
18 statistically superior to placebo beginning at about
19 day 2 and continuing through day 7. A similar
20 response was seen with Naproxen. These results were
21 replicated in the two other osteoarthritis flare
22 studies as shown here and then here.
23 These are the conclusions of our pain
24 program. We believe the data indicates that Celecoxib
25 is efficacious as demonstrated by replicate studies

1 using two pain models. One an acute pain model
2 including three post-dental surgery studies, and then
3 a second model for short-term pain using OA flare.
4 The recommended dose is 100 or 200 mg bid, and for
5 acute pain, the data indicates that the second dose
6 may be administered as early as 4 hours after the
7 first dose.
8 I would now like to move into our
9 differentiation program, and begin with a review of
10 the general safety data collected from our clinical
11 trials. Our safety data base is very extensive and it
12 includes all study participants, whether they were in
13 pharmacokinetic studies, analgesia trials, arthritis
14 studies, or our long-term open label study. The long
15 term open label study allowed patients to receive
16 Celecoxib for up to two years in duration, but only
17 after they had completed participation in one of the
18 arthritis trials. There was a total of 18,000 study
19 participants in the program. However, because some of
20 these patients are repeats, they rolled out of the
21 double-blind studies into the open label. There were
22 13,000 unique subjects and patients.
23 Our general safety analyses included a
24 review of all serious adverse events and deaths, and
25 that is a review of the incidents of all adverse

1 events and withdrawals through adverse events. Our
2 focus will be on the North American clinical trial,
3 because that was the majority of the data base. The
4 patients in those studies are most representative of
5 the intended population of Celecoxib. We also look at
6 the long-term open label safety data and we also look
7 at laboratory results.
8 Here we show the incidence of serious
9 adverse events in the three treatment group. So we
10 have placebo, all doses of Celecoxib, and then the
11 active comparator. We expressed the data in terms of
12 crude incidences, and then in the lower line we
13 express it in terms of number of events per 100
14 patient years of exposure. And whether the data is
15 expressed as crude incidence or as patient years, you
16 really see that the incidence of serious adverse
17 events was low and similar across the treatment group.
18 The two body systems that accounted for
19 the most serious adverse events included the GI system
20 and the cardiovascular system. And again, we see that
21 these incidences are low and similar across the
22 treatment groups. I would like to point out that when
23 we refer to GI serious adverse events here, we are not
24 talking about the ulcer complication data that I will
25 be referring to later in the presentation. These

1 types of serious GI events included hospitalizations
2 for hernia repair, hospitalizations for appendectomy,
3 et cetera.
4 Here we show the incidence of deaths
5 expressed as crude incidences for the three treatment
6 groups and expresses events per 100 patient years.
7 Again, they were very low and similar across
8 treatment. The majority of deaths were due to
9 cardiovascular problems, and again we see that that
10 was low and similar among the treatments.
11 Here we show from the North American
12 trials a listing of adverse events that occurred with
13 greater than or equal to 5 percent incidence in any
14 treatment group. And how we express the data is
15 placebo. In this column, we show Celecoxib at full
16 therapeutic doses, and then we show Celecoxib at the
17 highest dose, 400 mg bid, and then the NSAIDS.
18 Now here we show the incidence of any
19 adverse event, and with placebo it was about 55
20 percent. With Celecoxib, it was about 60 percent. And
21 with NSAIDS, it was 67 percent. The incidence of any
22 adverse event with Celecoxib was statistically greater
23 that placebo. The incidence with NSAIDS was
24 statistically greater than placebo, but also greater
25 than that seen with Celecoxib. The incidence of any

1 adverse event, and even the incidence of any of the
2 specific adverse events was not dose-related in the
3 Celecoxib-treated patients.
4 Here we showed the incidence of withdrawal
5 due to adverse events from these trials, with an
6 incidence of greater than or equal to .5 percent.
7 With placebo, withdrawals due to any event was 6
8 percent, Celecoxib about 7 percent, and NSAIDS about
9 10 percent. And the difference between NSAIDS and the
10 other groups was statistically significant. Also, some
11 of the specific adverse events, the incidence of
12 withdrawal due to specific adverse events such as
13 abdominal pain was statistically greater with NSAID
14 compared to Celecoxib or placebo.
15 Now here we compare the incidence of
16 adverse events in the Celecoxib patients who were in
17 the North American trials compared to the incidence of
18 these events and the long-term open label trial. I
19 would like to remind you that the North American
20 trials were three months in duration whereas the open
21 label experience allowed patients to go up to two
22 years. Despite this increase in exposure to the drug,
23 the incidence of adverse events in the long-term trial
24 really was not much higher than what was seen in the
25 three month trials.

1 I would now like to review the laboratory
2 data with a focus on the liver and the kidney. Here
3 we show the incidence of elevations in ALT, and we
4 express the data as the percent of patients who had an
5 ALT level which was three times the upper limit of
6 normal and also express it as 8 times the upper level
7 of normal. As seen, the incidence of these elevations
8 was not different between Celecoxib and placebo.
9 However, the experience with Diclofenac indicates
10 that the incidence of elevations was statistically
11 greater than Celecoxib for both three times the upper
12 limit and 8 times the upper limit.
13 Here we show the incidence of abnormal
14 renal function tests, and we show representative renal
15 function tests such as creatinine to get an index of
16 overall renal function, potassium indicating
17 management or handling of electrolytes, and also uric
18 acid, which is an indication of tubular function
19 and/or systemic urate metabolism. And how we express
20 the data is the percent of patients who had a moderate
21 abnormality in any one of these tests or an extreme
22 abnormality in one of these tests. And what you can
23 see in terms of extreme values, they were non-existent
24 for creatinine and potassium in each of the groups,
25 and for uric acid, they were rare and not different

1 across treatments. For moderate changes or moderate
2 laboratory test results, the incidences were again low
3 and similar across the treatment groups.
4 The conclusions of our safety program, our
5 safety analysis, are shown here. We believe the data
6 indicate that Celecoxib is well tolerated. Its safety
7 profile with short-term use and long-term use are
8 similar. The incidence or overall incidence of
9 adverse events with Celecoxib are less than with
10 NSAIDS but higher than with placebo. Laboratory test
11 results were similar to that seen with placebo. And
12 the incidence of elevated liver function tests was
13 lower than that seen with Diclofenac.
14 Now as Dr. Isakson showed earlier, we now
15 understand that COX-2 is constitutively expressed in
16 both the kidney and the brain. So we did some
17 analyses that I would like to review with you on these
18 specific organ systems. Here we show the incidence of
19 adverse events related to the central nervous system
20 or psychiatric adverse events that occurred in greater
21 than or equal to 5 percent of patients in the North
22 American arthritis trials. As seen, the incidence of
23 these types of events was actually statistically
24 greater in the placebo group than either the Celecoxib
25 or the NSAID group. And this was largely due to the

1 higher incidence of headaches with placebo compared to
2 the active treatments.
3 I would now like to move on to the effects
4 of Celecoxib on renal function. To assess this, we
5 looked at renal-related adverse events, effects on
6 blood pressure, and we also conducted special studies
7 to look at the renal pharmacology of Celecoxib. And
8 these studies were conducted in healthy elderly
9 patients and in patients with chronic renal
10 insufficiency.
11 Here we show the incidence of renal-
12 related adverse events. As seen, the incidence for
13 any renal event was low, and it was somewhat higher
14 with Celecoxib and the NSAID, and that increase was
15 statistically significant compared to placebo. The
16 most common renal-related adverse event was peripheral
17 edema occurring in 1 percent of placebos and 2 percent
18 with Celecoxib and the NSAID. Now this incidence was
19 statistically significantly different from that seen
20 with placebo, but I would like to point out that the
21 incidence of the peripheral edema with Celecoxib was
22 not accompanied by weight gain, not accompanied by
23 blood pressure changes, and the incidence of the edema
24 was not dose-related. Withdrawals due to renal
25 adverse events were infrequent and similar across the

1 treatment groups.

2 Here we show an analysis of the effects on
3 blood pressure in the 12-week arthritis trials. And
4 what we are doing is comparing placebo with Celecoxib
5 and Naproxen. As seen, we show the baseline blood
6 pressures in terms of systolic and diastolic pressures
7 and then the mean change at the end of the study. As
8 you can see, the mean change was actually just a mild
9 decrease in systolic and diastolic pressure, but there
10 were no differences across the treatment groups in
11 terms of blood pressure changes during the study.

12 The objectives of our renal pharmacology
13 studies were to compare the effects of Celecoxib on
14 renal function versus placebo and Naproxen. As said
15 earlier, the studies were conducted in the healthy
16 elderly and patients with chronic renal insufficiency.
17 These studies were short-term in duration, ranging
18 from 7 to 10 days. The highlights of the results are
19 shown at the bottom of this slide. There were no
20 effects with Celecoxib on GFR. We did observe a
21 transient reduction in sodium excretion with
22 Celecoxib, and that occurred during the first 24 to 48
23 hours after starting dosing, but then it returned to
24 normal. And that was similar to what was observed
25 with Naproxen.

1 The conclusions of our renal program are
2 shown here. Renal adverse events were uncommon with
3 Celecoxib and similar to that seen with NSAIDS. There
4 were no effects on blood pressure. We did observe
5 transient reduction in sodium secretion, but that was
6 similar to what was seen with Naproxen. The incidence
7 of edema was low, and there was no evidence in the
8 overall program of any serious metabolic abnormalities
9 with either Celecoxib or the NSAID.
10 I would now like to move on to the effects
11 of Celecoxib on platelet function. We collected data
12 on bleeding-related adverse events, and we also
13 conducted specific platelet studies as described
14 earlier by Dr. Isakson. Here we show the incidence
15 of bleeding-related adverse events from the North
16 American trials. And as seen, when you look at any
17 bleeding-related event, the incidence was low. And
18 although it was low, the incidence was statistically
19 greater with the NSAIDS compared to Celecoxib or
20 placebo. Withdrawals due to bleeding-related adverse
21 events were infrequent and similar across treatment
22 groups.
23 As Dr. Isakson described earlier, we
24 conducted studies to compare Celecoxib to placebo and
25 NSAIDS in terms of platelet function. There were five

1 studies conducted in healthy volunteers. The duration
2 of these trials ranged from a single dose to up to 10
3 days of repeat dosing. The results were that there
4 was no effect with Celecoxib at two times the full
5 therapeutic dose on either platelet aggregation,
6 Thromboxine B2 production, or on bleeding time. These
7 results have resulted in us concluding that bleeding
8 related adverse events with Celecoxib are uncommon,
9 but significantly lower than NSAIDS and similar to
10 placebo. there is no effect on serum Thromboxine
11 levels, platelet time or bleeding time at two times
12 the full therapeutic dose. The platelet studies
13 support the COX-2 sparing effect of Celecoxib.
14 I would now like to move on to the GI
15 program. We have been conducting clinical trials for
16 about 13 years to assess the effects of NSAIDS on the
17 GI mucosa. We have done multiple endoscopy trials and
18 we have also done a major GI complication study which
19 many of you may know as the mucosa trial. We used
20 that broad experience over the past 13 years to design
21 a program to assess the effects of Celecoxib on the GI
22 tract, and we used many of the people who helped us
23 develop those concepts in our particular program, and
24 many of those consultants are here with us today.
25 This slide shows the results of the mucosa

1 trial that we conducted several years ago, and what we
2 did is we looked at the probability of developing an
3 upper GI event, that is, an ulcer complication, a
4 bleeding or a perforation over six months. And what
5 we found is that NSAIDS had a probability of a GI
6 event that was significantly reduced by the
7 administration of exogenous prostaglandins. However,
8 I would like to point out in order to show this
9 difference or test for the difference, it required
10 about 4,000 patients per treatment group.
11 Our GI program was a prospectively
12 designed program. To look at the effects of Celecoxib
13 on GI symptoms, we also conducted endoscopy trials in
14 patients with arthritis, and we also did do analyses
15 of upper GI complications with Celecoxib. This slide
16 shows the incidence of GI adverse events from our
17 North American trials. Here we show any GI events.
18 As you can see, the incidence of GI events with the
19 NSAIDS was statistically greater than both placebo and
20 Celecoxib. Actually, it was about close to 30 percent
21 greater than with Celecoxib. Celecoxib did have a
22 higher incidence of GI adverse events than placebo.
23 We also show the four most common GI adverse events,
24 and as you can see the incidence of these events with
25 the NSAID was statistically greater than both

1 Celecoxib and placebo for dyspepsia, abdominal pain
2 and nausea.
3 Here we show the incidence or the GI
4 events that caused withdrawal from study participation
5 in greater than or equal to .5 percent of patients.
6 And as you can see, the incidences were low. There
7 was no difference between Celecoxib and placebo, but
8 the incidence of withdrawal due to GI adverse events
9 was statistically greater with the NSAIDS compared to
10 both placebo and Celecoxib. And this was largely due
11 to the higher incidence of abdominal pain.
12 I would now like to move onto the GI or
13 the endoscopy studies. We believe that endoscopic
14 ulcers are, in fact, surrogates for upper GI ulcer
15 complications, and the rationale for that conclusion
16 is shown here. We know that NSAIDS reduce mucosal
17 prostaglandins and cause ulcers. Ulcers can result in
18 bleeding, perforation or gastric outlet obstruction.
19 We have shown over the years by administering
20 exogenous prostaglandins you can reduce both the
21 endoscopic ulcers and the ulcer complications by about
22 50 percent over a 6-month period.
23 We conducted five endoscopy studies, and
24 I would like to first show you the endoscopy studies
25 that were conducted in OA and RA patients as part of

1 our pivotal trial program. In each of these studies
2 -- one of them was in RA patients and one was in OA
3 patients and they were pivotal trials. In addition to
4 reaching an arthritis flare, the patients underwent a
5 baseline endoscopy and were only considered to be
6 candidates for the trial if they did not have an ulcer
7 at baseline. They were then randomized to receive
8 either placebo, Naproxen or Celecoxib at doses ranging
9 from either 50 mg bid up through 400 mg bid. At the
10 end of 12 weeks of therapy, an endoscopy was again
11 performed.
12 This slide shows the mucosal grading scale
13 that were used in all these trials. Scores ranged
14 from zero to 7 with 7 indicating an ulcer. An ulcer
15 was defined as a break in the mucosa of unequivocal
16 depth of at least 3 mm in diameter. Again, as we have
17 shown earlier, there were about 200 patients per
18 treatment group per study, and in this set of trials
19 there was about 2,300 study participants. And here we
20 show the results from these two trials expressed as
21 incidence of gastroduodenal ulcers over the 12-week
22 period. As seen in each study, the incidence of
23 ulcers with Naproxen was about 25 percent. In the
24 placebo group, the incidence of ulcers was about 4
25 percent, and that was replicated. The incidence of

1 ulcers with Celecoxib, irregardless of dose, was not
2 statistically different from placebo and there were no
3 differences across the Celecoxib doses. Obviously,
4 the incidence of ulcers with the Naproxen was
5 statistically greater than the other treatments.
6 This slide expresses the incidence of
7 ulcers in the stomach and the duodenum for one of
8 those two trials, and this is representative of what
9 happened in the other trial. Again, you can see the
10 incidence of ulcers with Naproxen is statistically
11 greater than the other treatments in the stomach and
12 the duodenum. The incidence of ulcers with placebo
13 was not different than what was seen with Celecoxib
14 again in the stomach or the duodenum.
15 We conducted a 6-month study to look at
16 the incidence of ulcers with Celecoxib. This was part
17 of this -- these endoscopies were part of the study
18 that I described earlier to look at the durability of
19 Celecoxib. In this trial, patients received Celecoxib
20 at 200 mg twice a day or Diclofenac SR 75 mg twice a
21 day. The patients in this study did not undergo a
22 baseline endoscopy, and the advantage of that was that
23 that mimics better really medical practice, in that
24 patients before going on a drug for treating their
25 arthritis are not routinely endoscoped. But then at

1 the end of 6 months, we did endoscope the patients and
2 compared the incidence of ulcers in the two treatment
3 groups.
4 This slide shows the results. At the end
5 of 6 months in the Diclofenac group, there was an
6 incidence of ulcers of about 15 percent. The
7 incidence of ulcers with Celecoxib was only 4 percent.
8 That incidence with Celecoxib was very similar to what
9 we saw in the 3-month study, and again very similar to
10 what was seen with placebo. This slide breaks out the
11 data in terms of ulcers in the stomach and the
12 duodenum, and as you can see, we can see a higher
13 incidence of ulcers with Diclofenac compared to
14 Celecoxib.
15 We also conducted serial endoscopy trials.
16 This slide shows the rationale of why we did so.
17 Asymptomatic ulcers due to NSAIDS may form and reheal
18 but without detection, especially if there is a long
19 interval between endoscopies. Therefore, serial
20 endoscopies might better estimate the true incidence
21 of ulcers with the given agent as opposed to simply
22 doing a baseline and end of study endoscopy. We
23 conducted two serial endoscopy trials. They were
24 conducted in patients with OA or RA. The patients
25 underwent baseline endoscopy and only were entered if

1 they did not have an ulcer at baseline. They received
2 Celecoxib at 200 mg twice a day or an NSAID at a full
3 therapeutic dose of an NSAID. Endoscopies were then
4 performed after 4 weeks, 8 weeks, and 12 weeks.
5 Similar to the other studies that we have conducted,
6 there were approximately 200 to 300 patients per
7 treatment arm per study, and there was about 1,600
8 patients who participated.
9 This slide shows the cumulative incidence
10 of gastroduodenal ulcers in our first trial in which
11 we compared Celecoxib to Diclofenac 75 mg bid and
12 Ibuprofen 800 mg tid. We express the data as
13 cumulative incidences over the given period -- so zero
14 to 4 weeks, zero to 8 weeks, and zero to 12 weeks. As
15 seen, the cumulative incidence of ulcers with
16 Ibuprofen was statistically greater than Celecoxib at
17 each of the time points. The next slide breaks the
18 data out in terms of gastric ulcers and duodenal
19 ulcers. Again, the incidence with Ibuprofen is
20 greater than Celecoxib in both stomach and the
21 duodenum. And when you look at the incidence of
22 duodenal ulcers, we now see that the incidence of
23 these ulcers is statistically greater with Diclofenac
24 compared to Celecoxib at each of the intervals under
25 question.

1 This slide shows the results of the second
2 serial endoscopy trial in which we compared Celecoxib
3 to Naproxen at a dose of 500 mg twice a day. And as
4 with the previous trial, what we see is the NSAID has
5 a cumulative incidence of ulcers which is greater than
6 that seen with Celecoxib. The results of the gastric
7 and duodenal ulcers is virtually the same as seen
8 before.
9 The conclusions of our endoscopy program
10 are shown here. We conducted endoscopies in close to
11 5,000 patients with arthritis. The incidence of upper
12 GI ulcers seen with Celecoxib were really similar to
13 what was seen with placebo, and this was replicated.
14 However, the incidence of the ulcers was statistically
15 lower compared to Naproxen, Diclofenac and Ibuprofen.
16 Finally, I would like to move into our
17 analyses of upper GI complications. Although we
18 believe there is a rationale for using ulcers as
19 surrogates or endoscopic ulcers as surrogates for
20 upper GI complications, we also did collect these
21 types of data. This slide shows the process that we
22 went through for collecting this very important
23 information. We first formed an external committee of
24 expert consultants who are with us today who
25 prospectively defined what is an upper GI ulcer

1 complication. During the Celecoxib program,
2 investigators would report to the external committee
3 any potential cases that they thought were ulcer
4 complications. The committee then reviewed the data
5 from the individual patient in light of the
6 prospective definitions and then assessed whether or
7 not they believed the complication had, in fact,
8 occurred. The committee was blinded to the patient's
9 treatment and what study the patient was participating
10 in throughout this entire process.
11 The complications committee included Dr.
12 Fred Silverstein, who is the principle investigator
13 for the mucosa trial, and Dr. Naurang Agrawal and Jay
14 Goldstein, who also have extensive experience in the
15 whole area of GI toxicity.
16 The basic categories of GI complications
17 that they defined included bleeding, perforation, and
18 gastric outlet obstruction. Our program really was
19 very extensive. We collected information from our
20 controlled trials and from our open label trial. The
21 controlled trials included 14 studies that were in
22 arthritis patients, or all the 14 studies that we used
23 with arthritis patients. This involved about 11,000
24 patients and about 1,700 patient years of exposure.
25 In the open label program, which was one study, at the

1 time we submitted the NDA, there was about 4,500
2 patients accounting for about 2,700 patient years of
3 exposure. We subsequently completed a safety update
4 on that study and the number of patients has increased
5 to about 5,000, and the number of patient years of
6 exposure has also increased to about 5,000.
7 This slide shows the results of the ulcer
8 complication analyses from the controlled trials.
9 Here we show the various treatments -- placebo,
10 Celecoxib and the NSAIDS -- the number of patients,
11 the number of ulcer complication events that were
12 identified by the committee, the Kaplan-Meyer estimate
13 of the cumulative event rate through 12 weeks of
14 therapy, the number of patient years of exposure, the
15 number of events expressed as per 100 patient years of
16 exposure and then the calculated annual incidence of
17 these events. As seen, the annual incidence of
18 complications associated with NSAIDS was about 1.68
19 percent. The incidence of complications with
20 Celecoxib was .2 percent. That difference was
21 statistically significantly different. You will note
22 that there were no events in the placebo group, but I
23 would like to point out that there were only 200
24 patient years of exposure to placebo compared with
25 about five times those numbers of years of exposure

1 with Celecoxib.

2 This slide shows the ulcer complication
3 analysis from our open label program. We show the
4 number of patients at time of NDA and safety update.
5 There were 7 events identified at the time of NDA, and
6 that increased to 9 by the time of the safety update.
7 As shown, the calculated annual incidences in both
8 cases was .26 percent and .18 percent. And this is
9 very similar to what we saw in the controlled trials
10 as shown on the previous slide of about .2 percent.

11 This slide shows the conclusions of our GI
12 program. We believe that the data indicate that the
13 NSAID class labeling for Celecoxib is obviated,
14 because Celecoxib was similar to placebo in terms of
15 the incidence of upper GI ulcers and the incidence of
16 ulcer complications. In addition, compared to NSAIDS,
17 Celecoxib showed a significant reduction in the
18 incidence of GI symptoms, the incidence of upper GI
19 ulcers, and again the incidence of ulcer
20 complications.

21 To summarize our differentiation program,
22 we also showed that Celecoxib had no effects on
23 platelet function, whereas NSAIDS do inhibit platelet
24 function. Celecoxib had no effects on liver function
25 tests compared to NSAIDS and especially Diclofenac,

1 which did increase liver function tests.

2 So in summary, we have demonstrated that

3 by targeting COX-2 and eliminating the effects on COX-

4 1, we have achieved our clinical goals. We have

5 developed a compound with efficacy for arthritis and

6 pain but without the GI and platelet effects seen with

7 NSAIDS. These two properties indicate that clinically

8 Celecoxib is a specific COX-2 inhibitor. Thank you.

9 CHAIRMAN ABRAMSON: Thank you. Are there

10 questions for Dr. Geis? Can I just ask one question

11 for clarification? The numbers of patients that had

12 endoscopy at 3 months versus 6 months?

13 DR. GEIS: It depended upon the particular

14 trial. Endoscopies were scheduled. So in the studies

15 where we had a baseline and a 3-month endoscopy, all

16 patients underwent the baseline endoscopy. If they

17 withdrew early for any reason, they were scoped at the

18 time of early withdrawal, or we also allowed for

19 scoping for cause at any time, and that was similar

20 across the whole program.

21 CHAIRMAN ABRAMSON: Dr. Harris?

22 DR. HARRIS: I may have missed it, but can

23 you give me an idea in the post-dental pain studies

24 how many patients withdrew -- the percentage of

25 patients that withdrew because of lack of efficacy and

1 the comparison with the active group with Naproxen and
2 placebo?
3 DR. GEIS: Yes. We can show a slide if we
4 would like to show data on a Kaplan-Meyer of
5 withdrawals over time. So I can show that. Could I
6 have the slide, please? Here we show the percent of
7 patients remaining in the study, and this is in the
8 first two dental pain trials. And by remaining in the
9 study, we mean they did not require rescue medication
10 after receiving their particular treatment. Here we
11 show that the placebos drop out, and here you can see
12 the Naproxen and the Celecoxib. Of interest, at 12
13 hours you have about the same proportion of patients
14 remaining in the study with Celecoxib at the 200 mg
15 and the 100 mg in this study and for the 200 mg in
16 this study. The next slide, I believe, shows the
17 third dental pain trial. And again, we can see these
18 are the dropouts in the various treatment groups
19 because of requiring rescue medication.
20 CHAIRMAN ABRAMSON: Dr. Liang?
21 DR. LIANG: On slide 56, the neuro-psych
22 and CNS adverse effects, these were asked of subjects
23 in these trials in sort of a review of symptoms?
24 DR. GEIS: Sure. The question, as I
25 understand it, was in the slide that I showed on the

1 incidence of CNS and psychiatric adverse events, were
2 these spontaneously reported by the patients or were
3 the patients questioned about it. As with all the
4 adverse events that we collect, this was based on just
5 whether -- it was up to the investigator whether they
6 question the patient or whether the question
7 spontaneously talked about the adverse event. So what
8 we did is just anything, whether the physician or the
9 patient complained about something, it was considered
10 an adverse event.
11 DR. LIANG: Could I just have a follow-up?
12 CHAIRMAN ABRAMSON: Sure.
13 DR. LIANG: How was hypertonia -- how did
14 that come about? Can you describe that?
15 DR. GEIS: The various terminologies that
16 we use on the slides are the Huwart Dictionary codes,
17 and there is a match between what is written in the
18 text in the case report form to a particular Huwart
19 code. We sort of wondered what that meant too. And
20 when we went back and we looked at the actual text on
21 the CRF's, it really indicated sort of like muscle
22 cramping was usually what was happening and then it
23 was coded as hypertonia.
24 DR. LIANG: what about cognitive problems?
25 DR. GEIS: The cognitive problems were

1 just as shown on the slide. We can bring up that
2 slide. I believe we have that.
3 DR. LIANG: Well, there were none.
4 DR. GEIS: There were none? There were
5 some reported, but they were very rare. Because that
6 slide shows the incidence of greater than or equal to
7 .5 percent, I believe. So there were some, but they
8 occurred less than .5 percent of the time in a given
9 patient.
10 DR. LIANG: But the patient had to have
11 thought about it.
12 DR. GEIS: Well, that is true too. That
13 is true too.
14 CHAIRMAN ABRAMSON: Dr. Silverman?
15 DR. SILVERMAN: I would point out about
16 the cognitive question, we do have an ongoing clinical
17 trial in Alzheimer's with batteries of cognitive
18 testing, and that will really be a decisive
19 prospective analysis of behavior.
20 CHAIRMAN ABRAMSON: Okay. May I just
21 pause for a second? We are going to modify the agenda
22 and take the next 10 or 15 minutes for open questions
23 by the panel for any of this morning's speakers. So
24 I don't know, Dr. Needleman, if you want to make a
25 comment now or after that session.

1 DR. NEEDLEMAN: I think we may as well go
2 ahead to the questions.
3 CHAIRMAN ABRAMSON: Okay. Dr. Silverman?
4 DR. SILVERMAN: My question has to do with
5 the healing of ulcers, as there is spontaneous
6 healing. Was this looked at at all and what
7 percentage of patients changed in your cumulative
8 study? You have about a 30 percent incidence. How
9 many were new at the end, that sort of data as a
10 breakdown, per 4-week group?
11 DR. NEEDLEMAN: I think the way we will
12 proceed with questions -- I will try to triage it and
13 bring it together. That one specifically the relevant
14 issues will be the clinical data. I don't think that
15 there is -- we have seen no indications at all in our
16 preclinical packages that there is any interference.
17 Steve, do you want to come forward?
18 DR. GEIS: As I understand the question,
19 it is was there -- how did we affect healing of ulcers
20 in the program. We have asked that question,
21 especially since the literature suggests COX-2
22 regulation is important for healing. So I would like
23 to show you the analysis that we did which we think
24 solves this issue. Could I have the first slide,
25 please?

1 So what we looked at is -- as I will just
2 to remind you that at baseline patients were allowed
3 in the study if they had lots of erosions, just as
4 long as they didn't have an ulcer. So what we said
5 was were those erosions getting worse during the study
6 on Celecoxib or were they not changing or were they
7 actually the same. And what we did is we took
8 patients who had erosions at baseline and also who
9 were HP positive. Because we figured erosions plus HP
10 positive means up-regulation of COX-2. And if it is
11 up-regulated and you inhibit it, that is where you are
12 going to see the problem. We also only analyzed non-
13 aspirin users to get that causative factor out of the
14 way as well.
15 The analysis is shown on this slide. So
16 what we have are non-aspirin users who were HP
17 positive in the placebo, Celecoxib and the NSAID
18 group, and we look at the percent of patients who
19 worsened in terms of their GI score, didn't change, or
20 improved over the course of the study. And as you can
21 see, there is really no difference between what we saw
22 with Celecoxib and placebo, and that was somewhat
23 different than what you saw with the NSAID. So what
24 we are seeing is you are not seeing them getting any
25 worse and you are not seeing any change different from

1 what you see with placebo.

2 CHAIRMAN ABRAMSON: Okay. Dr. Fernandez-

3 Madrid --

4 DR. GEIS: Dr. Fred Silverstein was going

5 to make a comment, if that is okay, on these types of

6 data.

7 CHAIRMAN ABRAMSON: Okay.

8 DR. SILVERSTEIN: It is a very important

9 question obviously because we are all interested in

10 that. I would ask for slide 90, please. I just want

11 to show you the results of the ulcer data at 6 months

12 in a comparison of Diclofenac to Celecoxib and use

13 that to draw one conclusion. What you can see is the

14 Celecoxib group had an ulcer incidence of

15 approximately 4 percent. This is the same incidence

16 that was seen in the shorter term Celecoxib studies

17 and in the studies at 1, 2 and 3 months.

18 And I would propose from studies such as

19 the Whalen study from the New England Journal that if

20 an NSAID ulcer occurs and if there is interference

21 with healing, it can persist for months. And if that

22 were the case, I would expect that that number would

23 be increasing. Because you would be accumulating

24 ulcers which, in fact, were not healing clinically.

25 And the fact that it is staying the same suggests to

1 me that that recurrence and healing which may occur is
2 not accumulating with Celecoxib, and that in fact
3 there is no interference with healing.
4 And one other set of slides, 491, please.
5 This is a little bit detailed, but we did look at the
6 scoring system which occurs with the Lanza system,
7 which is a clever zero to 7 system, and compared what
8 happened from baseline to week 12 for a placebo,
9 Celecoxib and one of the NSAID comparators. It is a
10 little hard to see this from the slide, but basically
11 there was not significant worsening with the placebo
12 and Celecoxib. And in fact you can see that there was
13 an increase in ulcerations here occurring with
14 Naproxen. So we didn't see any sign that with
15 Celecoxib that the scores were getting worse in the
16 12-week endoscopy. So this is a third piece of
17 evidence in addition to what Dr. Geis showed in
18 patients with erosions that the endoscopic scores
19 didn't seem to be getting worse.
20 CHAIRMAN ABRAMSON: We have a question
21 over here first, Dr. Fernandez-Madrid.
22 DR. FERNANDEZ-MADRID: On the CNS effect,
23 I want to follow up that. What was the average age of
24 the patients and what proportion of patients were age
25 over 65?

1 DR. GEIS: We can call up a demographic
2 slide. But just as they are finding it, the mean age
3 in the OA program was 65 years. In the RA program it
4 was 55 years. The slide that we are going to pull up
5 will show you --
6 CHAIRMAN ABRAMSON: Excuse me, Steve. I
7 don't mean to interrupt you, but what I would like to
8 do for this period is if the question can be answered
9 to the satisfaction of the person who asked it without
10 a slide, I would like to do it that way.
11 DR. GEIS: Okay. Sure.
12 CHAIRMAN ABRAMSON: Otherwise, we won't
13 get all our questions out.
14 DR. GEIS: Okay.
15 CHAIRMAN ABRAMSON: So, I am sorry, go
16 ahead.
17 DR. GEIS: So it was 65 years in the OA
18 program and 55 years in the RA program was the
19 average.
20 DR. FERNANDEZ-MADRID: Fine. On the OA
21 study, what were the clinical features of the OA
22 patients in terms of the severity of the disease?
23 DR. GEIS: We could pull up a slide and
24 look at it, but just in summary in terms of patients
25 global assessment, all the patients, if you have the

1 5-point scale of good, very good, fair, poor, very
2 poor, they were fair or poor or very poor, with the
3 vast majority of them being around in the range of
4 fair and poor on the patients global.
5 DR. FERNANDEZ-MADRID: How about in the
6 radiological classification category and minorities?
7 DR. GEIS: We did not do radiological
8 exams.
9 DR. FERNANDEZ-MADRID: So you really don't
10 know how severe was the osteoarthritis?
11 DR. GEIS: Only severity based on
12 symptoms.
13 CHAIRMAN ABRAMSON: Dr. McCarthy?
14 DR. MCCARTHY: I would like to return to
15 Dr. Silverstein for a moment if possible. He claimed
16 that in slide 90 there is no indication that with
17 prolongation of time there is an increase in lesions
18 with Celecoxib. But in fact slide 95, which is the
19 slide showing 4-week endoscopy intervals, it does show
20 a progressive increase of about 3, 6, and 9 percent in
21 the 4, 8, and 12-week data. Could you comment on
22 that?
23 DR. GEIS: Should we pull that one up?
24 CHAIRMAN ABRAMSON: Yes, please.
25 DR. SILVERSTEIN: Yes, Denis, I can. It

1 is a good point. What in fact is happening is that it
2 is a cumulative incidence. So the ulcers may be
3 coming and then going. So you are not seeing the
4 incidence at 12 weeks. You are seeing the cumulative
5 incidence by 12 weeks from endoscopies at 4, 8, and 12
6 weeks. So your observation is a good one, but it is
7 not that the point prevalence at 12 weeks is going up.
8 It is accumulating.
9 DR. MCCARTHY: Right. But what it says is
10 that the rate of accumulation is a constant on
11 Celecoxib.
12 DR. SILVERSTEIN: Right. And I think the
13 point Dr. Alexander is making is that it may well be
14 on placebo at the same time.
15 CHAIRMAN ABRAMSON: Dr. Silverman?
16 DR. SILVERMAN: Changing to renal events.
17 Some of the renal events are very rare, including
18 papillary necrosis, ATN. How many numbers of patients
19 would you estimate you would have had to study to come
20 up with some of these rare events?
21 DR. NEEDLEMAN: Let's call Dr. Whelton,
22 Andy, from Johns Hopkins.
23 DR. WHELTON: Thank you very much. You
24 are absolutely correct. In fact, it is not possible
25 in the extent literature to give you a precise

1 incidence figure, but it presumably is of the order of
2 more than 50,000 to 100,000 patient exposures over a
3 prolonged period of time. In contradistinction to the
4 issue, for example, hemodynamically mediated acute
5 renal failure, we would anticipate that once in about
6 every 200 patients who received a 5 to 7-day course of
7 treatment we would see such an event. But the
8 papillary necrosis and nephrotic syndrome would be
9 rare events and would only realistically be picked up
10 in post-marketing surveillance programs.
11 CHAIRMAN ABRAMSON: Dr. Liang?
12 DR. NEEDLEMAN: Furthermore, I think our
13 preclinical evidence is clear that even in chronic
14 exposure to animals we didn't see renal papillary
15 necrosis.
16 DR. LIANG: I don't think the NDA has any
17 data on serum bicarb. Do you have data on potassium
18 and chloride?
19 DR. NEEDLEMAN: Yes, we do. Let me call
20 Andy Whelton back to the podium. You get your
21 exercise this morning.
22 DR. WHELTON: Thank you very much. I must
23 indulge the Chairman and ask Dr. Abramson if I may
24 show a few slides.
25 CHAIRMAN ABRAMSON: Yes. This is an issue

1 that needs to get addressed, please.

2 DR. WHELTON: Thank you very much. If you

3 would give me kindly the nod for that. May I

4 therefore start with slide #1071. I do need to take

5 a moment or two to review the innuendos of changes of

6 chloride that might be anticipated as reflectors of

7 changes with bicarbonate. So we do need to start with

8 a very, very brief note of physiology. Taking you

9 back to the dim distant days when you were worried

10 about these issues.

11 The essence of it is in the extracellular

12 fluid space, one will recall that all of us have

13 positively charged cations in the form of sodium, and

14 I am showing concentration here simply as meq/l, and

15 potassium, taking them as the dominant positive

16 charges. Counterbalanced by chloride, bicarbonate

17 designated as HCO_3 here, and the anion gap which would

18 reflect charges of protein, et cetera. If chloride

19 has a tendency of going up, as I am showing by this

20 arrow, the reciprocal change one would anticipate

21 would be a reduction of bicarbonate and ergo maybe a

22 suggestion of a systemic acid-base change. Similarly,

23 were chloride to go down, one would anticipate that

24 bicarbonate or the anion gap, maybe accumulation of

25 the anions of endogenously accumulating acids would go

1 up.

2 The next slide, please, would be 759.

3 This is to take a look at the entities that may

4 reciprocally elevate chloride with a reduction of

5 bicarbonate. And as we look through the data base,

6 this was an issue of concern for us. Entities such as

7 diarrhea, the use of acetazolamide was an issue in two

8 patients in the data base, through to questions such

9 as an impact on the tubule would be of relevance, and

10 then importantly because of the size of the data base,

11 laboratory errors or variances.

12 Next let's look at slide 760, please.

13 This is going to give us an appreciation of what

14 happened to the serum chloride recognizing that in the

15 data base we do not have bicarbonate. The a priori

16 reason for that being that we know from 30-plus years

17 of prior experience that nonsteroidals do not

18 routinely and indeed even rarely cause systemic acid-

19 base problems. What we see here in the first 12 weeks

20 of course gives us the comparison with placebo and an

21 active comparator in the form of Naproxen. I am

22 showing here the mean concentration of chloride at

23 baseline and then at 6 months the change, at 9 months,

24 12 months, and 15 months. And one can see that

25 progressively there tends to be a reduction rather

1 than an increase suggesting therefore that long-term-
2 wise, we are not seeing an impact on the bicarbonate
3 fraction in the ECF.
4 And if I might have the next one, 764,
5 please. I have zeroed in here on the 22 patients in
6 our data base in the controlled component of the trial
7 who manifested a serum chloride equal to or greater
8 than 110 at baseline. In actual fact, the cut for the
9 upper limit of chloride in the laboratory, the
10 reference laboratories we used in these studies, was
11 112. But taking it at 110 and asking how many went up
12 by 2 millimoles during the study. One can see if you
13 take the number of patients and correlate that with
14 the total in our data base, it is about 5 placebos per
15 1,000. It also is about 5 Celecoxib per 1,000 and 5
16 active comparators per 1,000. And if we ask over this
17 period of time what happened to them, approximately
18 one half ended up with a lower chloride and one half
19 with a slightly elevated one. And the essence of it
20 is we had only two patients at a level of 115 or
21 greater, one with Celecoxib and one with Naproxen.
22 My interpretation of this overall is that
23 we are not seeing short-term or long-term anything to
24 suggest a modicum of a red flag of the development of
25 a systemic acid-base disorder.

1 Yes. I am sorry, I heard a short question
2 on potassium.
3 DR. LIANG: That was my original question.
4 I left potassium and went to chloride.
5 DR. WHELTON: In fact, potassium -- we
6 looked at a level of 6 meq or greater to see if there
7 was an abnormality because a substantial number of
8 patients in our data base were concurrently receiving
9 antihypertensives that might have elevated the
10 potassium. In the entire data base, we do not see any
11 elevation in any patient at a level of 6 or greater.
12 We do see using a cutoff of 5.4 as the upper limit of
13 normal, a very few patients that fit into such a
14 category. In essence, there is no problem with
15 potassium. Hypokalemia was seen very rarely, but only
16 intercurrently with significant diuretic use.
17 CHAIRMAN ABRAMSON: Thank you. I think we
18 will hold the questions for now. Dr. Needleman, do
19 you want to make a final statement?
20 DR. NEEDLEMAN: Rather than call up the
21 slides, you notice by the number that we haven't
22 finished all our digits on those slide numbers.
23 CHAIRMAN ABRAMSON: I know. We could
24 spend a couple of days.
25 DR. NEEDLEMAN: Well, it is from the

1 school of thought that data is what speaks.

2 CHAIRMAN ABRAMSON: Right.

3 DR. NEEDLEMAN: We really wanted to

4 present you this comprehensive clinical program or

5 preclinical program that in its magnitude is unique,

6 over 13,000 patients, 10,000 endoscopies in 4,500

7 patients, 5,000 years of patient experience. The

8 preclinical and the clinical data confirms the

9 hypothesis and points to the unique safety of these

10 agents and really dictates an opportunity because we

11 are talking about rational drug design now, mechanism

12 based. And it is against a backdrop of decades of use

13 of NSAIDS where patients were exposed to profound

14 inhibition of both COX-2 and COX-1, and now we have an

15 agent which spares the COX-1 part of the problem and

16 what was the unmet medical need. The reality was it

17 was dealing with 107,000 hospitalizations in the

18 United States and 16,500 deaths dominated from these

19 studies by the COX-1 side effects. That is what we

20 wanted to present you this morning.

21 CHAIRMAN ABRAMSON: Thank you. And

22 thanks, Searle, for a very excellent presentation this

23 morning. We will reconvene in 15 minutes at 10:35.

24 (Whereupon, at 10:22 a.m. off the record

25 until 10:39 a.m.)

1 CHAIRMAN ABRAMSON: We will begin the
2 second part of this morning with presentations by
3 members of the FDA. We will begin with Dr. James
4 Witter. Is Dr. Witter with us?
5 DR. WITTER: Good morning. The function
6 of my presentation has been described as I am the
7 wafer around the oreo cookie. So we will decide which
8 you like better. And now my talk is complete. I do
9 realize that today is not March 24, but what I would
10 like to do is just set this meeting in some context
11 and remind everyone that we have discussed similar
12 types of issues relating to the safety and toxicity
13 with COX-2 agents back in March 24 of this year. If
14 you are so inclined, it is on the Agency's Website.
15 I just wanted to give you a brief rundown
16 here. You go to the search command and type in
17 advisor committee minutes and follow through the
18 Freedom of Information minutes to CDER and Arthritis
19 Advisory Committee, and you will come up to a 372-page
20 document, and I have in parentheses here 1, 2, 3. For
21 some reason, the first page shows 1, 2, 3. So just
22 continue on to the next page and the next slide and
23 what you will see is a -- what we had discussed with
24 the committee at that time. I have gone back and kind
25 of just reminded us, for example, of some of the

1 questions that we had previously submitted to the
2 Arthritis Advisory Committee. The degree to which,
3 for example, endoscopic studies can distinguish
4 between currently available nonsteroidals and also the
5 degree of correlation with clinical outcomes.
6 Some of the comments that I thought were
7 of interest and that I thought I would share today
8 were that endoscopic studies generally are
9 underpowered to significantly address the clinically
10 relevant outcomes issue. The measurable, in this case
11 endoscopic, drives out the important clinical
12 outcomes, and endoscopy is a surrogate for long-term
13 outcomes.
14 We also discussed a variety of other
15 issues. As you can see here, renal safety,
16 reproductive, bone, cartilage, effects in children and
17 on skin. Really I think what this was intended to do
18 was to discuss things in more of a theoretical
19 abstract. We didn't really have the data at that
20 time. And I think what we were doing was trying to
21 understand the distribution -- from understanding the
22 distribution of the function of COX to how we might
23 predict some of the safety related outcomes and
24 efficacy, for example.
25 Well, today it is not the problem of data.

1 We have lots of data. I thought you might find this
2 of interest that if you make some rough calculations
3 here of the volumes, and there were 452 volumes, this
4 did not include case report forms and safety updates,
5 for example. And if you figure that by the time you
6 do a priority review and by the time you get things
7 actually to the committee, you have about 4 months.
8 You can see that there was a lot of work that had to
9 be done and this is just to remind me to thank all of
10 the reviewers who are behind the scenes and all the
11 supporting staff. This is really a massive effort no
12 matter how you look at it.
13 Now in spite of how many patients we might
14 actually study in an NDA, we all are aware that we
15 can't study everyone. The question really is what
16 would happen with any kind of compound once it is
17 registered -- what will happen in the real world. And
18 here, for example, is a patient that I know was not in
19 the NDA. It is a 61-year-old female who has a history
20 of severe cardiovascular disease and is on Warfarin.
21 She had a several day history of pain, which I will
22 leave undescribed, and tried some over-the-counter or
23 non-narcotic analgesics without success and the pain
24 persisted. She finally tried an over-the-counter
25 nonsteroidal. This was not aspirin, she knew not to

1 mix aspirin and Warfarin, and developed black stools,
2 became light-headed, was admitted to the hospital and
3 was transfused with three units of packed cells.
4 So, again, I think what this really brings
5 to mind is the reason -- one of the major reasons that
6 we are here, the real public health issues that we are
7 trying to address, which we are very familiar with,
8 and those are the clinically relevant outcomes. For
9 example, the ARAMIS data base has been updated here,
10 as you heard earlier, that it is predicted that in
11 arthritis patients, which would then be a conservative
12 estimate, the number of NSAID-induced gastropathy will
13 result in 107,000 hospitalizations and over 16,000
14 deaths. And, of course, the agency has in its GI
15 warning section sentences describing the rate of onset
16 of these. For example, in approximately 1 percent of
17 patients for 3 to 6 months and about 2 to 4 percent in
18 patients treated for one year. So we are familiar
19 with the importance of the clinically relevant events,
20 but there is not necessarily an agreement on how these
21 should be defined or analyzed in a large and simple
22 trial, for example.
23 This is kind of a take on a common little
24 adage. The way to a person's joints is through their
25 stomach. I think as our friend illustrates, there is

1 a frustrating link between trying to decrease the role
2 of prostaglandins in contributing to pain and
3 inflammation in the joint from the role prostaglandins
4 have in contributing to health in the stomach. And
5 really breaking this link requires demonstrating that
6 improved GI safety does not do so at the price of
7 sacrificing efficacy.
8 So in other words, if we look at COX-2
9 agents as they might compare against NSAIDS and
10 wondering how Celecoxib in this case might represent
11 COX-2 agents, do we have comparable efficacy in terms
12 of pain, OA and RA in this instance, to nonsteroidals,
13 and if we have that comparable efficacy, then do we
14 have superior safety in the regards of GI, renal,
15 platelet, and the overall safety. And as you consider
16 issues of efficacy and safety, I think we need to keep
17 in mind that if you say something is similar to
18 placebo, that is not the same as saying that it is
19 equivalent to placebo, and we will discuss that a bit
20 later.
21 All of this really leads us to labeling,
22 which is the major way that we can distinguish between
23 anecdotal stories and personal experiences from what
24 actually has been documented. This comes from the
25 draft OA and RA guidance document to kind of give us

1 a feel for what we are trying to achieve when we write
2 a label. And we really want to talk about the
3 documented benefits, and I should really say risks
4 here as well of a product.
5 So, for example, with these types of
6 compounds early on, there have been hopes for some
7 great things. For example, in the Wall Street Journal
8 in May of 1996, it was predicted and stated that these
9 might be the Holy Grail that has eluded arthritis
10 researchers for decades, medicines that ease pain and
11 may actually slow the debilitating course of the
12 disease. But we have to put that in context of what
13 actually are achievable goals in the development of
14 any particular compound. For example, if you look at
15 the draft RA guidance document, and we have laid out
16 in that document the various claims that you can try
17 to attain for a new compound. For example, the prior
18 slide would suggest prevention of structural damage.
19 There is also a claim for prevention of disability,
20 induction of remission, and induction of a complete
21 clinical response, a major clinical response, and
22 finally reduction in the signs and symptoms of RA.
23 This is, in fact, what Celecoxib has -- the indication
24 for which they are seeking today.
25 Similarly, if we look at the draft OA

1 document, we have the possibility of OA prevention,
2 improvement in OA structure, or improvement in OA
3 symptoms. Once again, Celecoxib is going for the
4 first one, improvement in OA symptoms. So there is no
5 suggestion that we are going for any kind of disease
6 modification.
7 So in terms of what we actually have for
8 the OA indication, I think we can say at this point in
9 time that Celecoxib at doses of 100 to 200 mg bid is
10 more efficacious than placebo. There is no obvious
11 efficacy advantage of 200 mg bid. 100 mg bid and 200
12 mg given once a day appear to have comparable
13 efficacy. Overall then, Celecoxib is comparable to
14 Naproxen 500 mg bid, and we see that patients
15 generally are still symptomatic. In other words, you
16 saw that patients still have pain. There is a similar
17 incidence of withdrawal due to lack of treatment
18 effect and time to withdrawal between Naproxen and
19 Celecoxib. This was in the randomized controlled
20 portion of the trial. Interestingly, the open label
21 experience shows that about 70 percent of the patients
22 increased their dose, something that we had discussed
23 in the March meeting of dose creep.
24 For the RA indication, we can say that at
25 100 to 400 mg bid, Celecoxib is more efficacious than

1 placebo, and once again there does not appear to be an
2 obvious efficacy advantage of 400 mg bid. Celecoxib
3 is comparable, again, to Naproxen 500 mg bid and has
4 a similar incidence of withdrawal due to lack of
5 treatment effect and time to withdrawal as Naproxen.
6 This, again, was in the randomized control portion.
7 Again in the open label experience, Study 024, most of
8 the patients -- again 70 percent -- increased their
9 dose up to 400 mg bid. This again illustrates what I
10 think is the concept of dose creep.
11 So we have also been asked to kind of
12 differentiate to address the question as to whether
13 COX-2 agents represent a different class. I think if
14 we do that, we need to ask whether a single agent can
15 represent a class. What if there are more potent
16 inhibitors and what if they have a different mechanism
17 of action. We also need to be aware of if COX-2
18 agents are considered as a class, how should we
19 describe them. And for any NDA really, how much are
20 we testing the drug, the theory of the drug, or both?
21 So, for example, if you go back to the
22 March advisory committee and try and do a theoretical
23 safety advantage for COX-2 inhibitors, you might come
24 to the conclusion that if in an area like platelets
25 where the COX-2 is not present you would get one

1 result, A, which in this case we would say would be
2 comparable to placebo. If, on the other hand, you go
3 to an area where COX-2 is present, such as the
4 kidneys, the bone, the brain -- and the list is
5 growing really as our understanding of COX-2 is
6 improving -- you might get a result, C. And that
7 would be not necessarily different than NSAIDS. And
8 in the middle you may have stomach, where in a normal
9 situation of health it would not necessarily be the
10 same as if you have an H-pylori infection, so the
11 results could be intermediate. Those are some things
12 that need to be considered.
13 So today for the presentations, we have
14 Dr. Averbuch talking about pain, Dr. Throckmorton
15 talking about renal safety, Dr. Goldkind talking about
16 GI safety, Dr. Yang preclinical, and Dr. Lee PK.
17 DR. AVERBUCH: Thank you, Jim. Can I have
18 the first slide, please? For the approval of new
19 medication for the treatment of acute pain, these are
20 the usual regulatory requirements. We require at
21 least replicative evidence of efficacy in at least two
22 pain models, of which one will be the single dose
23 model when patients will not need more than one or a
24 few doses of the medication, and the other model will
25 be a short-term medical dose study over several days

1 for patients requiring short-term therapy.

2 Now keeping these requirements in mind, we

3 can now look at how Celecoxib performed in this NDA.

4 So for the single dose requirement, the sponsor has

5 conducted three dental pain studies. All of them were

6 randomized, double-blind parallel group placebo and

7 active control. Celecoxib was tested in doses of 25,

8 50, 100, 200 and 400 mg, and the active comparators

9 used were Ibuprofen 400 mg in one study and Naproxen

10 Sodium 550 mg in the two other studies.

11 Now don't try to read this slide. It is

12 much too busy. This is just to give you the general

13 concept of the pain relief scores over time. You can

14 see that in all three studies, the pain relief curves

15 over time were pretty much the same.

16 So here we are looking at the pain relief

17 results for dental pain study 027. The blue line is

18 the Naproxen 550 mg and the green line is the

19 Celecoxib 200 mg and the yellow line is Celecoxib 100

20 mg and the red line is the placebo. So the results

21 demonstrated that Celecoxib in doses of 100 and 200 mg

22 as shown in these studies were statistically

23 significantly better than the placebo in the treatment

24 of acute pain starting at 45 minutes to one hour post-

25 medication and continuing through 7 to 8 hours.

1 Now although the active comparators were
2 used in these studies mainly to validate the studies,
3 one cannot ignore the fact that the active comparators
4 were statistically significantly better than Celecoxib
5 in the treatment of acute pain in all doses tested.
6 So with this study you can see the Naproxen 550 mg,
7 which is statistically significantly better than
8 Celecoxib starting at 30 minutes and continuing
9 through 4 hours.
10 This is the second dental pain study,
11 study 070. Again, Celecoxib in doses of 400 mg, the
12 green line, 200 mg the purple line, 100 mg the yellow
13 line, were all statistically significantly better than
14 the placebo, the red line, and Naproxen Sodium was
15 statistically significantly better than Celecoxib at
16 doses of 100 and 200 mg beginning at 45 minutes and
17 continuing through 5 hours.
18 This is the third dental pain model.
19 Again, the results are very consistent. Celecoxib 200
20 mg is better than the placebo. And Ibuprofen 400 mg
21 is statistically significantly better than Celecoxib
22 beginning at 45 minutes and continuing through 3
23 hours. So this is our take on the single dose
24 studies.
25 Three multiple dose short-term studies

1 have been included in the development program for
2 Celecoxib, of which the sponsor showed you only one.
3 Two of them were post-orthopedic surgery pain studies,
4 of which one was stopped after an enrollment of only
5 one patient, and the reason given was that the
6 comparator selected was not considered to be suitable
7 for that pain model.
8 The second post-orthopedic surgery was --
9 this is the one that the sponsor showed you. During
10 the first 24 hours, some positive scattered and
11 inconsistent findings of efficacy in favor of
12 Celecoxib have been detected. However, eventually
13 neither Celecoxib nor Darvocet, which was the active
14 comparator, separated statistically from placebo over
15 the study period, which was 3 to 5 days.
16 The third study was a post-general surgery
17 study which was terminated following an interim
18 analysis that again showed no efficacy of all
19 treatment arms.
20 What other pain assessments have been
21 carried out during the development program? With the
22 exception of three studies in all OA and RA studies,
23 pain was first measured a week after the initial dose.
24 And obviously studies that measure pain for the first
25 time a week after drug administration cannot provide

1 evidence of efficacy to support the treatment of acute
2 pain. We have three OA studies that measure pain at
3 bedtime beginning on the first study day and
4 continuing for 7 days. Two of them were knee OA
5 studies and one was a hip OA study, and they all used
6 the American Pain Society, the APS measure.
7 Without going into any great detail, the
8 APS pain measure is using five questions to assess
9 pain during the past 24 hours. So here you can see
10 the results of the APS course at bedtime of day one
11 compared to placebo. We have here the five APS
12 questions -- pain in the past 24 hours, pain now,
13 worse pain in the past 24 hours, average pain in the
14 past 24 hours, and pain interference in life during
15 the past 24 hours. The green check signs denote that
16 Celecoxib was statistically significantly superior
17 than the placebo, while the red X's denote that
18 Celecoxib was not superior to placebo.
19 So we can look at hip OA study 054. In
20 these studies, Celecoxib was statistically superior to
21 placebo in 4 of the 5 APS questions and was not
22 superior to placebo in one question. On the other
23 hand of the scale, you can look at knee OA study 020,
24 in which Celecoxib was not superior to placebo in any
25 of the five APS questions, and in between there is

1 knee OA study 021 in which Celecoxib was superior to
2 placebo in one question and was the same as the
3 placebo in the four other questions.
4 In general, we can say that at bedtime on
5 day 2 through day 7, Celecoxib was statistically
6 better than the placebo in most of the APS questions
7 in all three studies.
8 So now going back to the first slide of my
9 presentation, just to remind you that we do require
10 evidence in both the single dose model and the
11 multiple dose short-term studies. Now we can
12 summarize what was this NDA able to demonstrate to us.
13 So as regard to the single dose part of the
14 requirement, we have three dental pain single dose
15 studies that provide evidence of efficacy for
16 Celecoxib in the management of acute pain versus
17 placebo. The post-op short-term multiple dose studies
18 failed to provide evidence of efficacy for Celecoxib
19 in the management of acute post-surgical pain. And
20 the OA studies showed some positive results that may
21 be regarded as supportive but still inconclusive
22 evidence of efficacy in the treatment of acute pain.
23 And for these reasons, we believe that Celecoxib at
24 this time has not yet met the requirements to gain the
25 treatment of acute pain indication. Thank you.

1 CHAIRMAN ABRAMSON: Are there any
2 questions for Dr. Averbuch? Thank you. I am sorry,
3 one question.
4 DR. LOVELL: I have one question. In the
5 labeling for acute pain that this drug is going for,
6 would it be for all kinds of pain such as headache,
7 abdominal pain, generalized pain, or would it be
8 specific to certain kinds of pain?
9 DR. AVERBUCH: Well, a drug can have both
10 of them or as many of them as you like. It all
11 depends on what the data show. So you can have
12 treatment of acute pain in general. You can have the
13 indication of treatment of headache or dysmenorrhea or
14 pain of osteoarthritis, as in this case.
15 DR. THROCKMORTON: The Division of Cardio-
16 Renal Drug Products was asked to perform a safety
17 review on the NDA for Celecoxib to assess the effects
18 of Celecoxib on the renal system. As the primary
19 renal medical reviewer, I would like to summarize the
20 conclusions of our division.
21 To do this, I used -- to perform the
22 review, two trial data bases were used primarily. The
23 first was the North American Osteoarthritis/Rheumatoid
24 Arthritis trials which have been previously described.
25 These were both placebo and active comparator,

1 nonsteroidal controlled, with follow-up for up to 12
2 weeks. The second data set came from the open label
3 OA/RA trial number 024. In this trial, all patients
4 received Celecoxib and follow-up was for longer than
5 12 weeks for up to one or more years.
6 My talk will be broken into three parts.
7 First I would like to discuss some of the measured
8 renal lab abnormalities. Then I would like to discuss
9 two of the more common "renal adverse events"
10 associated with nonsteroidal use in the past.
11 Finally, I would like to end with a discussion of some
12 of the occurrence of severe renal adverse events in
13 the NDA data base.
14 I would like to begin my discussion with
15 hyperchloremia and hypophosphatemia. I have broken
16 the data into a little bit different than Dr. Whelton
17 used. In this case, this table shows the incidence of
18 hyperchloremia, as measured there or hypophosphatemia
19 as measured there, occurring at any point during the
20 controlled trials, so anytime during the 12 weeks. As
21 you can see, the incidence of these abnormalities was
22 increased in both the Celecoxib and the active control
23 groups relative to the placebo group. The next slide
24 shows this for the hyperchloremia data in graphic
25 form. As you can see, the incidence rate for placebo

1 is differentiated for hyperchloremia from the
2 incidence in both Celecoxib and active control.
3 As Dr. Whelton elucidated, when an
4 increase in serum chloride is measured, there is a
5 possible concern regarding acid-base balance. As he
6 also stated, no measurements of serum bicarbonates or
7 arterial pH's were collected as part of this NDA,
8 limiting further assessment of this.
9 The final lab abnormality I would like to
10 review was, again, the incidence of increased blood
11 urea nitrogen as defined by a BUN of greater than 20
12 mg per deciliter at any time during the 12-week
13 controlled trial data base. As you can see, again,
14 the incidence of this elevated BUN was increased in
15 both the Celecoxib and the active control groups
16 relative to placebo. The next slide breaks this data
17 down by the dose of Celecoxib as well as the active
18 control nonsteroidal comparator. The point here is
19 that at all dose levels of Celecoxib, 100 mg per day
20 up to 400 mg per day, and the active control can all
21 be distinguished from the incidents in the placebo
22 group.
23 The next slide is our conclusions
24 regarding renal lab abnormalities. Celecoxib and
25 nonsteroidals were associated with a higher incidence

1 of renal abnormalities than were the placebo group.
2 As regards acid-base balance, in the absence of serum
3 bicarbonate data, an effect of Celecoxib and the
4 comparator nonsteroidals on acid-base balance cannot
5 be excluded.
6 Next I would like to turn my attention to
7 the occurrence of "common renal adverse events"
8 beginning with hypertension, which has been reported
9 to follow the use of nonsteroidal use in the past.
10 This table shows the incidence of reported adverse
11 events, hypertension and aggravated hypertension,
12 which were the two forms that were reported by the
13 investigators, as well as the combination of the two
14 in the third row. As you can see, in the third row in
15 the combination of both adverse events, the incidence
16 of this combination adverse event reporting was
17 increased in both the Celecoxib group and in the
18 active control.
19 The next slide shows this same data in
20 graphical form. And if you concentrate on the white
21 bars, which is the placebo rate and the rate in the
22 Celecoxib groups and the rate in the active control,
23 the point here again is that for Celecoxib and active
24 control, the incidence rates of hypertension can be
25 distinguished from placebo. In addition, in the

1 controlled trial data base, withdrawals for
2 hypertension took place for six patients in the
3 Celecoxib group at a rate of 0.1 percent compared with
4 no patients in the placebo group and one patient in
5 the active control, again a nonsteroidal which have in
6 the past been associated with aggravated hypertension.
7 In addition, in the long-term trials, there were four
8 patients withdrawn for worsening hypertension.
9 In conclusion, similar to nonsteroidals,
10 there is an association between the use of Celecoxib
11 and hypertension.
12 Next, I would like to turn to edema as
13 another "common adverse event." This light highlights
14 the incidence of edema, and the two rows that are
15 highlighted are peripheral edema and again a
16 combination of the reported adverse events for all
17 edemas. As you can see for both peripheral edema --
18 here, here and here -- and for all categories of
19 edema, the incidence of reported adverse events in the
20 Celecoxib group and the active control group are
21 higher than in the placebo group. The next slide
22 shows the peripheral edema data. Again, over the dose
23 range used, 100 mg and up to 400 mg of Celecoxib per
24 day, and the active control, and it again makes the
25 point that at all doses the incidence rates for

1 peripheral edema were higher in Celecoxib and the
2 active control than in placebo.
3 Similar to nonsteroidals, there is an
4 association between the use of Celecoxib and edema,
5 especially peripheral edema.
6 Finally, regarding the occurrence of
7 severe renal adverse events, which I will abbreviate
8 as SAEs. The renal SAEs in the controlled trial data
9 base were rare. And as you can see the numbers, two
10 in the placebo group, 7 in the Celecoxib group, and 1
11 in the active control group. The percentages are
12 small. You can see there is a small increase in
13 Celecoxib over placebo. The renal SAEs reported for
14 Celecoxib, however, were aggravated hypertension,
15 cardiac failure, uremia, and renal calculus. Again,
16 adverse events one might expect to see reported for
17 nonsteroidals.
18 In the long-term data base, there were 12
19 patients that had renal SAEs reported. These included
20 acute renal failure, aggravated hypertension,
21 pyelonephritis, renal calculi, hyponatremia and
22 hypokalemia. Finally, the reasons for withdrawals in
23 the long-term trials included acute renal failure,
24 azotemia, or increased BUN and creatinine for six
25 patients, worsened hypertension in four cases, edema

1 for 10 cases, and proteinuria or hematuria in two
2 cases. Again, a pattern that would be consistent with
3 what might be expected for nonsteroidals. There were
4 no cases of either papillary necrosis or nephrotic
5 syndrome detected in the data base.
6 In conclusion then, the pattern of renal
7 adverse events in the NDA data base is consistent with
8 the pattern seen with nonsteroidals. No cases of
9 either papillary necrosis or nephrotic syndrome were
10 detected in the data base. I would agree with Dr.
11 Whelton that given the extremely low incidence of
12 these adverse events that has been reported with
13 nonsteroidals -- some of them are too low even to have
14 had incidence rates estimated -- a larger data base
15 would be needed to adequately assess the incidence of
16 these potential -- I say potential, not documented
17 severe renal injuries following Celecoxib. There was
18 no existence to suggest a unique renal toxicity of
19 Celecoxib not seen with nonsteroidals in this NDA. No
20 evidence exists that any renal toxicity associated
21 with nonsteroidals occurs at a higher incidence rate
22 with Celecoxib.
23 In conclusion then, I would like to take
24 two statements that appear in the briefing document
25 from the sponsor and follow them with some of the

1 divisions which I think will show the similarity of
2 our conclusions. One -- these are from the sponsor --
3 the available data suggests that the renal effects of
4 Celecoxib may be similar to nonsteroidals. And two,
5 the incidence of peripheral edema and all other renal
6 adverse events with Celecoxib was similar to
7 nonsteroidals. Statements of the Cardio-Renal
8 Division and myself include, the available data
9 suggests that the renal effects of Celecoxib and
10 nonsteroidals are similar. The available data
11 suggests that the renal effects of Celecoxib and the
12 comparator nonsteroidals are clearly distinguished
13 from placebo. And finally, use of Celecoxib and the
14 comparator nonsteroidals are associated with both
15 worsened hypertension and edema. The frequency of
16 severe renal injury following Celecoxib abuse remains
17 to be determined. Thank you.
18 CHAIRMAN ABRAMSON: Thank you. Any
19 questions? Dr. Harris?
20 DR. HARRIS: In assessing your data, is
21 there, in terms of Celecoxib versus placebo, the
22 things like peripheral edema and hypertension, did it
23 reach statistical significance in terms of the
24 separation?
25 DR. THROCKMORTON: Well, since this was a

1 safety analysis and I am not sure that either study
2 was powered for that, you would be talking about
3 nominal statistical significance rather than any true
4 statistical significance. In peripheral edema, I
5 believe it did. But you should probably check that.
6 The sponsor would know those better than I do.
7 CHAIRMAN ABRAMSON: Dr. McCarthy?
8 DR. MCCARTHY: Were any of the severe
9 renal SAEs associated with binge drinking, volume
10 depletion or sodium depletion?
11 DR. THROCKMORTON: I looked for other drug
12 administrations. I was particularly interested in
13 interactions with some of those. Binge drinking, I
14 don't remember at all. And volume depletion, nothing
15 marked. But that one I am a little less clear on,
16 yes.
17 CHAIRMAN ABRAMSON: Okay. Thank you very
18 much. Dr. Goldkind?
19 DR. GOLDKIND: I am Larry Goldkind. I am
20 a member of the Division of Gastrointestinal and
21 Coagulation Drug Products and will briefly review the
22 upper GI safety data related to endoscopic studies for
23 Celecoxib. The overall talk will focus on these
24 issues. I would like to briefly review the overall GI
25 safety clinical development design by the sponsor.

1 The issue of class comparisons, as Dr. Witter had
2 mentioned, the question will arise can Celecoxib
3 represent all COX-2 inhibitors as a class, and the
4 same question needs to be asked of the NSAID
5 comparators used. The next issue is comparability to
6 placebo, and finally the issue of clinically
7 significant upper GI events.
8 First, the general overview of the
9 endoscopic studies. There was one initial small 7-day
10 pilot study performed followed by 5 pivotal studies.
11 Four of these pivotal studies were of 12 weeks
12 duration, two of which were placebo controlled. There
13 was one 24-week endoscopic trial. There were, as
14 mentioned by the sponsor, multiple comparators --
15 Naproxen, Ibuprofen and Diclofenac. And I am sure the
16 advisory committee is aware that this represents but
17 a subset of the universe of nonsteroidals available.
18 On the other hand, these are very commonly used
19 nonsteroidal anti-inflammatory agents and are felt to
20 represent a fair set of comparators to use in these
21 type of studies and the multiplicity should also be
22 noted.
23 Also the sponsor did have one endoscopic
24 study where a 2X dose was tested, 400 mg bid, in an
25 endoscopic study, which does give us a buffer of

1 endoscopic information on this drug. As mentioned by
2 the sponsor, it was a large design with over 4,500
3 patients randomized. I think a point worth making
4 also is that the study population chosen by the
5 sponsor was a good one. There were minimal
6 exclusionary criteria, which then left us with a valid
7 set of patients from which to draw conclusions on the
8 drug. Specifically, elderly patients, those with
9 heart disease, prior ulcer disease, prior GI bleeding,
10 the use of DMARD, and low-dose aspirin users were not
11 excluded. These are patients who we typically think
12 of as possibly at high risk for upper GI complications
13 of NSAIDS, and they were included in the studies.
14 On the other hand, the development program
15 did rely primarily on endoscopic data with its
16 limitations that have been discussed by the advisory
17 committee in the past. Endoscopic diagnosis, we have
18 to remember, while some view it as a gold standard
19 does rely on a visual assessment of ulcer size and
20 that does have inter-observer variability and is
21 somewhat subjective. The extent of endoscopic data is
22 limited to six months, and this is for a new molecular
23 entity with proposed chronic usage. Finally, there
24 was no plan for a statistically powered study of
25 clinically significant upper GI events.

1 The next issue is that of class
2 comparisons. Next slide.
3 Three studies were performed which
4 included Naproxen. All three of these did reveal a
5 statistically significant lower ulcer incidence in the
6 Celecoxib group at 12 weeks in both rheumatoid as well
7 as osteoarthritis patients. One study was performed
8 including Ibuprofen which revealed this same result,
9 a highly significant benefit to Celecoxib in both RA
10 and OA patients.
11 This is a table summarizing the pivotal
12 endoscopic studies, and really I would want to draw
13 attention to the issue of Diclofenac, which I hadn't
14 mentioned in the earlier slides, the third comparator.
15 One study here did reveal an important statistically
16 significant difference in the prevalence of ulcers at
17 6 months. However, study 71 did not reveal a
18 statistically significant difference in the study.
19 Next slide. I want to point out here that
20 study 41 was a prevalence study, as I will discuss
21 with the next slide, and study 71, which revealed no
22 statistical difference in ulcer rate at each of the
23 time points studied. The question is why these
24 inconsistent results.
25 Next slide. I just want to briefly review

1 some of the details of the study which may help us
2 draw conclusions, none of which will probably be
3 definitive, but I think it is important to understand
4 both studies. Study 71 did have more endoscopic data,
5 both in terms of the number of patients studied as
6 well as the number of endoscopies per patient. There
7 was a baseline endoscopy and patients with ulcers were
8 excluded. Then there was endoscopy performed at 4, 8
9 and 12 weeks in addition to endoscopies for cause or
10 at the termination of the study. This study was
11 carried out in the United States. It was large and
12 multi-centered.
13 Study 41 was an international study, also
14 large and multi-centered with a somewhat fewer number
15 of patients. It was a longer study at 24 weeks
16 compared to the 12 weeks. As Dr. Geis mentioned,
17 there was no baseline endoscopy performed, and the
18 final ulcer rates really give us more of a point
19 prevalence at 24 weeks rather than an ulcer incidence.
20 We know that patients entered these studies coming off
21 of nonsteroidals, and we all know that patients on
22 nonsteroidals will have a significant point prevalence
23 rate of ulcers.
24 Next slide. This is simply a graphic form
25 of the results. Ulcer prevalence, 4 versus 15

1 percent, with a P value of less than .001.

2 Next slide. In study 71, you can see that

3 at each data point -- 0 to 4, 0 to 8, 0 to 12, and

4 final endoscopy -- there was no statistically

5 significant difference between each group, although

6 the percentages themselves do indicate a trend.

7 Next slide. In summary, we have one

8 statistically significant study and one inconclusive

9 study with a trend in favor of Celecoxib. Next slide.

10 Again, looking at possible causes for these

11 inconsistent results, possibly the statistical

12 methodology, possibly the study design. Certainly

13 differing pharmacodynamic properties among NSAIDS and

14 specifically Diclofenac will have to be considered.

15 This begs the original question of class comparisons.

16 Would other untested NSAIDS perform similarly, better

17 or worse compared to Diclofenac or compared to the

18 other two comparators?

19 Next slide. The next issue to discuss is

20 that of comparability to placebo.

21 Next slide. Studies 21 and 22 were

22 designed to evaluate both efficacy and GI safety

23 defined by endoscopic data compared to the active

24 comparators and the powering of the studies and the

25 numbers of patients were based on that issue. There

1 was no statistical comparison to placebo stipulated
2 within the protocol.
3 Next slide. This represents merging both
4 of these two studies, these placebo-controlled
5 studies, and one can see that the P value begins to
6 approach statistical significance at .088. This data
7 is different than that shown by the sponsor earlier in
8 that this represents the final ulcer rate as opposed
9 to the 12-week ulcer rate. The sponsor did do a very
10 thorough job of ascertainment. And as mentioned
11 earlier, endoscopies that were performed at early
12 termination for any reason or for cause based on GI
13 symptoms were included within the final ulcer data in
14 addition to the scheduled endoscopies.
15 Next slide. A question comes up, does the
16 observed differences in ulcer rates between the
17 placebo and Celecoxib represent a biologically
18 meaningful difference. We need to note, obviously,
19 that this is a difference that will be reflected upon
20 in anticipated population of millions of patients.
21 Next slide. In conclusion, the difference
22 between placebo and Celecoxib associated ulcers has
23 not been fully addressed in the clinical safety
24 development program thus far. The next issue to be
25 discussed is whether such ulcer data is in fact the

1 ultimate question for us to be asking.

2 Next slide. This brings us to the issue

3 of clinically significant upper GI events.

4 Next slide. I am sure the advisory

5 committee is familiar with either this quote or one of

6 many similar ones. This comes out of the GI Clinics

7 of North America in 1996. "It is estimated that more

8 than 100,000 hospitalizations and 10,000 to 20,000

9 deaths per year are attributable to NSAID-related

10 gastrointestinal complications." I highlight the

11 gastrointestinal complications to point out that this

12 is a general term as opposed to specifically upper GI

13 events.

14 Next slide. What are the upper GI events

15 that are associated with such significant morbidity

16 and mortality? After reading the medical literature

17 on the subject and talking to some authors of some of

18 these articles, I feel like I am fair in at least

19 stating the opinions of some that we may not be able

20 to define it consistently in all studies in the

21 literature, but we know it when we see it. In fact,

22 there is no consistent definition of what represents

23 a clinically significant upper GI event in the medical

24 literature.

25 Next slide. Of course, we have to come up

1 with definitions if we are going to be doing studies,
2 and some of the functional definitions that have been
3 applied include PUB, meaning perforation, symptomatic
4 ulcer, or bleed; hematemesis, melena, any GI bleed.
5 Next slide, a hemodynamically significant
6 bleed, transfusion requiring bleed, gastric outlet
7 obstruction, hospitalization, and obviously death.
8 Surrogate markers such as endoscopically
9 identified ulcers are certainly of value and
10 biologically meaningful, but we all know that
11 asymptomatic endoscopic ulcer prevalence rates in
12 NSAID users occur at a fairly high rate while the rate
13 of clinically significant upper GI events is much
14 smaller.
15 Next slide. The degree of correlation
16 between ulcers and the serious morbidity and mortality
17 has not been well-established. One must assume that
18 the risk of clinically significant complications may
19 be influenced by many factors beyond the presence of
20 the surrogate endoscopic ulcer.
21 Next slide. There is no adequate
22 surrogate marker to replace the evaluation of NSAID
23 complications that are the source of morbidity and
24 mortality. What data do we have from this submission
25 regarding these events?

1 Next slide. This is a simpler slide than
2 the sponsors. I chose to simply represent the number
3 of events. But the number up here would put that into
4 perspective. It is not meant to suggest that there is
5 equivalence across, but more so to point out that I
6 feel that the data from the submission is not adequate
7 to really give us an annual incidence rate or
8 statistical information because these studies were of
9 short duration.
10 Next slide. Some of these events occurred
11 in studies of six weeks up to 24 weeks. Data was
12 merged from studies of differing durations, and most
13 importantly the total number of events accrued is too
14 small to establish a valid rate.
15 Next slide. And also equally important is
16 that these studies were not designed for statistical
17 comparison of clinically significant upper GI events.
18 As with the issue of placebo comparisons, adequately
19 powered trials are needed to test the hypothesis that
20 Celecoxib produces a lower incidence of clinically
21 significant upper GI events compared to NSAIDS.
22 Next slide. The studies in this NDA do
23 suggest that Celecoxib may produce fewer clinically
24 significant upper GI events than currently marketed
25 NSAIDS. However, to repeat an old refrain, there is

1 no substitute for a trial to test such an important
2 claim.
3 Next slide. Finally, our conclusion is
4 that we would recommend a Phase IV trial to study this
5 issue with appropriate clinically relevant endpoints.
6 Thank you.
7 CHAIRMAN ABRAMSON: Thank you. Since this
8 is going to be the basis of the discussion this
9 afternoon, I would like to move on to the next
10 presenter unless someone on the panel has a very
11 pressing question about the content.
12 DR. MCCARTHY: Just a very quick one. In
13 the two discrepant studies with Diclofenac, age has
14 been shown to be a very important predictor of both
15 prevalence and relative risk and absolute risk. Were
16 the age distributions similar, A, in the two trials?
17 In other words, is there an equal number of old people
18 in 041 and 071? And secondly, are they balanced with
19 regard to age within the two trials?
20 DR. GOLDKIND: I can only speak within
21 each trial. The demographic analysis revealed no
22 significant differences in age or in any of the other
23 risk factors that I mentioned early on within the
24 study. I honestly can't answer your question
25 comparing one study to the other. The sponsor might

1 be able to do that later.

2 CHAIRMAN ABRAMSON: Dr. Liang?

3 DR. LIANG: It is more of a philosophical

4 question. I am not a gastroenterologist, but it seems

5 to me that your criteria is almost proposing a trial

6 by fire. I mean, it is true that not all

7 endoscopically proven ulcers bleed. But I also

8 believe it is true that all bleeders have

9 endoscopically proven ulcers. So it seems to me that

10 you are really asking for something that may be

11 unrealistic, expensive, and putting patients at risk

12 to insist that we need to see blood before we can

13 approve it. I wonder why we can't get by this or what

14 the rationale is. Am I wrong about those two

15 assumptions?

16 DR. GOLDKIND: If your assumption is that

17 to approve the drug, we would have to have such a

18 trial, then my point was not well made. provability

19 of the drug is not suggested to rely on such data.

20 That is why it would be a Phase IV study. To claim

21 that clinically significant events occur with a

22 different incidence or significantly lower incidence

23 -- the MUCOSA study that was mentioned earlier is the

24 one that is always quoted in correlating clinically

25 significant upper GI events and endoscopically

1 identified ulcers. There are issues that we could go
2 into and weaknesses of that trial. But to rely on one
3 study to make the assumption that endoscopic ulcers
4 will be an adequate predictor is the question.
5 DR. LIANG: Well, it seems to me that the
6 MUCOSA trial may be, as you term it, a proof of
7 concept that endoscopically proven endpoints are
8 reasonable mapping to clinically significant health
9 events.
10 CHAIRMAN ABRAMSON: May I just interfere
11 or interrupt here for a minute? Because this will be
12 the grist for this afternoon's discussion. I will
13 take you off the hook right now and move on to the
14 next speaker.
15 DR. YANG: Good morning, everybody. I
16 would like to present the findings from the
17 preclinical study in the animals.
18 Next, please. In this NDA, the sponsor
19 submitted information in two single repeated dose
20 toxicity studies, carcinogenicity studies, a
21 reproduction toxicity study and a genotoxicity study.
22 Next slide. This slide shows the results
23 from the repeated dietary toxicity findings in the
24 mice. In the two-week dietary study, the doses used
25 are up to 20 times the human exposure as measured by

1 AUC zero to 24 hours for the male, and 10 times the
2 human exposure for the female. The major pathological
3 findings include GI perforated ulcer, kidney renal
4 tubular degeneration and regeneration, and the death
5 as a result of GI or kidney events. The number of
6 observed adverse effects level was 3.3 times the human
7 exposure for the male, about 3.6 times the human
8 exposure for the female.
9 In the 13-week dietary toxicity study, the
10 doses used are up to 8 times the human exposure for
11 the male and 11 times the human exposure for the
12 female. The major pathological findings include the
13 following -- GI perforated ulcer and kidney is
14 inconclusive as the finding was seen in the control,
15 and the deaths as a result of the GI perforation. In
16 the two-year carcinogenicity study, the doses used are
17 up to 2 to 3 times the human exposure. The results is
18 that it is non-carcinogenic. The GI and kidneys are
19 the major target organ with the lesion of the
20 perforated ulcer and pyelonephritis in the male only.
21 The tests were either results from GI or kidney
22 events. The number observed at the adverse effect
23 level was less than 1 times the human exposure.
24 Next slide. This slide summarizes the
25 toxicity findings in rats. In the 4-week oral

1 toxicity study, the dose used was up to 3.5 times the
2 human exposure for the male and 19 times the human
3 exposure for the female. The major pathological
4 findings include GI perforated ulcer and kidney
5 pyelonephritis. The tests either result from the GI
6 or kidney events. The number observed at the adverse
7 effect level was 1.8 times for the male and 9.5 times
8 the human exposure for the female.
9 In the 13-week oral toxicity study, the
10 dose used was up to 3.5 times the human exposure for
11 the male and 6.3 times the human exposure for the
12 female. The major pathological findings include
13 liver, transient increase of the AST, ALT and the SDH
14 levels. In the renal, renal papillary degeneration
15 was observed. The number observed at the adverse
16 effect level was 3.0 times human exposure for the male
17 and the 6.3 times the human exposure for the female.
18 In the 2-year carcinogenicity study, the
19 dose used was up to 5 to 10 times the human exposure.
20 The major findings include the following. It is not
21 carcinogenic and GI and kidney were the major target
22 organs, with the lesion of perforated ulcer and
23 pyelonephritis in the male only. The test resulted
24 from either GI or kidney events. The number of
25 observed adverse effect level was about 1.2 times for

1 the male and less than 1 times the human exposure for
2 the female.
3 Next slide, please. This slide presents
4 the summary toxicity findings in dogs. In the 7-day
5 IV study, the dose used was up to 8.5 times the human
6 exposure. The GI was the only pathological finding,
7 with lesions of pyloric duodenal ulcers. The number
8 observed at the adverse effect level was 4.4 times the
9 human exposure.
10 In the 4-week oral toxicity study, the
11 dose used was up to 10 times the human exposure. The
12 pathological findings are as following -- GI ulcer,
13 kidney papillary necrosis or pyelitis, skin
14 interdigital pyoderma or subacute abscess. In the
15 brain, it was inconclusive findings, lesions of
16 perivascular or periventricular lymphocytic
17 infiltration. The test was a result from the GI
18 event. The number of observed adverse effect level
19 was 2.8 times a human exposure.
20 In the 13, 26, and the 15-week oral
21 toxicity study, the dose used was up to 1 to 2 times
22 of human exposure. There were no remarkable
23 pathological findings because the maximum tolerable
24 dose was not achieved in these studies.
25 The effect of Celecoxib on the

1 reproduction system was included in the early
2 embryonic development study as well as teratogenic
3 study. This slide shows the results in the rate. At
4 the dose of up to 3.5 times the human exposure, there
5 is no effect on the fertility for the male. At the
6 dose of greater or equal to 5.4 times the human
7 exposure, the finding is as follows. Decreased live
8 fetuses in the implantation sites, and increased pre
9 and post-implantation loss. There is no effect on the
10 fertility. The number observed adverse effect level
11 was 3.7 times the human exposure.
12 This slide shows the data obtained from a
13 rat teratogenic study. At a dose equal or greater
14 than 6.2 times the human exposure, increased incidence
15 of diaphragmatic hernia in the 5th sternebrae
16 incomplete ossification was observed and slight
17 decrease of live fetuses. The number observed at the
18 adverse effect level was 2.2 times the human exposure.
19 This slide represents the data obtained
20 from the rabbit study. At doses greater or equal to
21 2.5 times the human exposure, decreased live fetuses
22 and increased incidence of ribs and sternebrae fused
23 and the sternebrae misshapen were observed. The
24 number observed at the adverse effect level was about
25 1.3 times the human exposure.

1 So in conclusion, I would like to put the
2 following information. In summary, the target organs
3 were observed in all of the studies. GI is the major
4 target organ. We could observe the toxicity finding
5 in the mouse, rat and dog, and the major pathological
6 lesions include ulcer perforation in the stomach and
7 the small intestine. This event is dose dependent.
8 In the kidney, the pathological findings could be
9 observed in the mouse, rat and dog. In the mouse and
10 rat, we see the lesion of pyelonephritis. This occurs
11 at a low incidence in the male only. In the dog 4-
12 week study, papillary necrosis and pyelitis was
13 observed at a low incidence. Liver, in the rate
14 study, a transient increase of AST, ALT and SDH was
15 observed with the microscopic lesion of the
16 centrilobular to midzonal hepatocellular enlargement.
17 The effect on the reproduction system
18 could be summarized as following. In the rat, pre and
19 post-implantation loss and decreased live fetuses in
20 the implantation sites. It is teratogenic in one of
21 the two studies because an increased instance of
22 hernia of the diaphragm was observed. In the rabbit,
23 increased post-implantation loss and decreased live
24 fetuses were noted. In the embryo fetuses, the data
25 showed that increased incidence of fetal alteration,

1 such as rib and the sternebrae fused and the
2 sternebrae misshapen.
3 The skin pathological finding was only
4 observed in the dog with the lesion of interdigital
5 pyoderma and the subcutis abscess. In the brain, it
6 is inconclusive. It is only observed in the dog with
7 the lesion of perivascular and the periventricular
8 lymphocytic infiltration.
9 There are several issues that need to be
10 addressed. The pathological findings in the animal
11 might be relevant to the human. GI findings in the
12 animal, does that correlate with the human upper GI
13 adverse events? The observation in the kidney, could
14 we draw any association to the kidney co-findings in
15 the humans? There is no information on the embryo
16 development or implantation for the human. What is
17 the possible association in the findings in the
18 animal? The pathological findings in the skin seen in
19 the dog, could that imply possible unique microbial
20 infection in the canine? The inconclusive
21 pathological findings in the dog brain, does that mean
22 something in the kidney or CNS disorder? This
23 concludes all my presentation. Any questions?
24 CHAIRMAN ABRAMSON: Were any of these
25 findings similar to what you would expect to find in

1 a traditional NSAID?

2 DR. YANG: Yes.

3 CHAIRMAN ABRAMSON: Any other questions?

4 Dr. Silverman?

5 DR. SILVERMAN: Just a simple question.

6 What does HE stand for?

7 DR. YANG: Pardon me?

8 DR. SILVERMAN: I am really not sure of

9 what human exposure refers to.

10 DR. YANG: Human exposure is measured by

11 the AUC zero to 24.

12 CHAIRMAN ABRAMSON: Dr. Felix-Madrid?

13 DR. FERNANDEZ-MADRID: I want to follow up

14 your question. In what way were these findings

15 different from the other multiple studies that you

16 have seen using other nonsteroidals?

17 DR. YANG: Generally speaking, these

18 lesions progress in time, and the doses use in these

19 studies generally speaking are much higher than the

20 regular NSAIDS.

21 CHAIRMAN ABRAMSON: Okay. Any other

22 questions? Thank you very much. Dr. Lee?

23 DR. LEE: Good morning. I will talk about

24 pharmacokinetic issues of Celecoxib that need

25 consideration by the committee. The pharmacokinetic

1 issues are related to elimination metabolism of
2 Celecoxib.
3 As presented earlier by Dr. Karim,
4 Celecoxib is predominantly eliminated by metabolism
5 with only approximately 3 percent of the dose excreted
6 and changed in urine and feces. The metabolism of
7 Celecoxib is mediated primarily via CYP 2C9 or
8 cytokine P45 2C9 isozyme. As for other P450 isozymes,
9 several inhibitors of CYP 2C9 have been identified.
10 Further, CYP 2C9 have been shown to exhibit
11 polymorphism resulting in poor metabolizers having
12 reduced CYP 2C9 enzymatic activities.
13 With that background information, we now
14 come to the issues. Our concern specifically relates
15 to use of Celecoxib in CYP 2C9 poor metabolizers, use
16 of Celecoxib concurrently with CYP 2C9 inhibitors, and
17 use of Celecoxib in hepatic impairment patients.
18 These are situations in which metabolic clearance of
19 Celecoxib is reduced resulting in higher than normal
20 plasma Celecoxib concentrations, and these are the
21 areas that we would like to have input from the
22 committee.
23 First, CYP 2C9 poor metabolizers. During
24 the clinical pharmacokinetic trials, 5 subjects were
25 found to have unusual high plasma Celecoxib

1 concentrations with the C-max and AUC ranging from 3
2 to 9-fold of expected values. Based on a total of 500
3 to 1,000 applicable subjects, these 5 subjects would
4 amount to approximately half to 1 percent of the data
5 base. I understand that the pharmacokinetic studies
6 were conducted in approximately 1,500 subjects.
7 However, because of the design of some studies, I had
8 to exclude several hundred subjects from this
9 calculation because they did not allow easy detection
10 of high plasma concentrations. It should also be
11 noted that in the published literature, it was cited
12 that CYP 2C9 poor metabolizers may amount to 8 percent
13 of the Caucasian population.
14 Two of the five subjects were genotyped
15 and were found to be poor metabolizers. There was one
16 subject with normal plasma Celecoxib concentrations
17 who was also genotyped and found to have normal copies
18 of CYP 2C9 genes. This slide shows the plasma
19 Celecoxib concentration profiles in these three
20 subjects. The lower curve represents the plasma
21 concentration of the normal subjects, while the other
22 two represent the two poor metabolizers. As you can
23 see, one of the poor metabolizers has very high plasma
24 concentrations. The unit for the concentration is in
25 mcg/ml because of the high values.

1 Because of this, although the data is
2 limited and the cause/effect relationship has not been
3 established, the findings are consistent with
4 expectations for poor metabolizers. Based on this,
5 our recommendation is that Celecoxib should be used
6 with caution in patients who are known or suspected to
7 be poor metabolizers.
8 Now I will talk about use of Celecoxib
9 concurrently with CYP 2C9 inhibitors. The sponsor has
10 conducted a drug interaction study with Fluconazole,
11 which is a known CYP 2C9 inhibitor. This study
12 investigated the effect of Fluconazole 200 mg qid
13 dosing for 7 days on the single dose pharmacokinetics
14 of Celecoxib at 200 mg dose. This slide compares the
15 two treatments. The lower curve represents Celecoxib
16 plasma concentrations after it was co-administered
17 with placebo. The upper curve represents plasma
18 Celecoxib concentrations after it was co-administered
19 with Fluconazole. Fluconazole apparently inhibits the
20 metabolism of Celecoxib resulting in a higher plasma
21 Celecoxib concentrations observed here. Based on
22 these results, we recommend that Celecoxib be
23 introduced at a reduced dose for patients who are
24 receiving Fluconazole.
25 Our last issue is use of Celecoxib in

1 hepatic impairment patients. The sponsor has
2 conducted a study in this patient population. The
3 severity of hepatic impairment was determined based on
4 Child-Pugh classification. Class I is mildly
5 impaired. Class II is moderately impaired. And Class
6 III severely impaired. You have seen this slide
7 earlier this morning. This slide compares the plasma
8 Celecoxib concentrations between normal subjects and
9 patients with mild hepatic impairment. You see a
10 higher concentration in the mildly impaired patients.
11 This slide again compares the plasma
12 Celecoxib concentrations between normal subjects and
13 patients who are moderately impaired in hepatic
14 functions. It is apparent that the plasma
15 concentrations in moderately impaired patients are
16 much higher and are actually also higher than in
17 patients with mild hepatic impairment. With these
18 results, you see the higher plasma Celecoxib
19 concentrations in hepatic impairment patients.
20 Numerically, these translate to an increase of
21 approximately 30 to 40 percent in C-max and AUC in
22 mildly impaired patients. For moderately impaired
23 patients, the C-max was more than doubled while the
24 AUC was almost tripled. The sponsor did not conduct
25 a study in severely impaired patients.

1 From the results, our recommendation is as
2 follows. For mildly impaired patients, the usual
3 dosage may be followed. For moderately impaired
4 patients, start with a reduced dose. Since we do not
5 have information, no data, on severely impaired
6 patients and we cannot predict the plasma Celecoxib
7 concentrations in these patients, we do not recommend
8 use of Celecoxib in these patients unless the sponsor
9 conducts a study to support its use.
10 To summarize, Celecoxib is predominantly
11 eliminated by metabolism with CYP 2C9. High Celecoxib
12 plasma concentrations may be observed in patients who
13 are poor metabolizers or in patients who are taking
14 Celecoxib concurrently with a CYP 2C9 inhibitor such
15 as Fluconazole, and also in patients who have hepatic
16 impairment. Our labeling recommendations reflect a
17 conservative approach to keep plasma concentrations
18 within clinical experiences and to reduce incidents of
19 adverse events. Thank you.
20 CHAIRMAN ABRAMSON: Thank you. I think
21 since this will also be a question for this afternoon,
22 we should wait on our questions for Dr. Lee until that
23 time. So thank you very much. Dr. Witter?
24 DR. WITTER: In much the same way that we
25 have discussed today how we can compare results with

1 using compounds, for example, like Diclofenac or
2 Naproxen and how they may represent what is commonly
3 called NSAIDS, what can we say about Celecoxib and how
4 it might represent what we may call the new class of
5 COX-2 agents. And can we then begin to characterize
6 efficacy. So can we say, for example, that the
7 analgesic efficacy of COX-2 agents is not quite what
8 you get with non-selective agents for acute pain? And
9 if this is the case, is that really a problem with the
10 pain models in this case, the dental pain model? Is
11 that a problem that relates to the nature of acute and
12 chronic pain? And this really gets at the issue of
13 COX-2 inductability. Or does it relate to potency or
14 selectivity issues?
15 Similarly, in short-term studies, there
16 does not appear to be any obvious advantage in the
17 treatment of OA and RA. But once again, will there be
18 any differences in long-term outcomes? Then again,
19 comparing Celecoxib as it may represent the class of
20 COX-2 agents in terms of safety characteristics, can
21 we begin to say the following? In areas where COX-2
22 is present, such as the kidney, they share toxicities
23 common to NSAIDS. Will there be new adverse events
24 with high grade long-term inhibition of COX-2 is one
25 of the questions that remains to be answered.

1 In areas where COX-2 may or may not be
2 present, such as the stomach, COX-2 agents may be
3 superior to NSAIDS, and we discussed some of those
4 results today, but not the same as placebo.
5 I think it deserves a little bit of
6 attention, what may be considered to be a semantic
7 battle here of similar versus equivalent. And I think
8 it is safe to say that saying two treatments are
9 similar does not necessarily mean that they are the
10 same. Statistically speaking, failing to show a
11 difference is not showing equivalence. Equivalence
12 requires that the hypothesis, treatment X and Y are
13 different, be rejected in a trial designed for this
14 purpose, and I hope the following three slides will
15 illustrate this.
16 Take for example study 21 and 22, which is
17 represented here. The green bars represent
18 differences of endoscopic ulceration rates between
19 Celecoxib and placebo, and they are plotted on an
20 axis, which you will notice that all the values are in
21 the beginning greater than zero. And also as you look
22 at these mean values or differences, it does not
23 appear that they are significantly different than
24 zero. However, when you put in and consider things
25 that actually represent -- these are small numbers of

1 events and you put in the variance here, in this case
2 the 95 percent confidence interval, and I would really
3 like to draw your attention to the upper 95 percent
4 confidence interval with the diamond on it. The
5 results look as follows.
6 If we were then to prospectively define in
7 an equivalence trial an area which is outlined here in
8 orange of a delta in which we would ignore that
9 difference -- in this case, I have just selected for
10 illustration plus or minus 4 percent -- you can see
11 that when you take into consideration the confidence
12 intervals, they do not fit within that shaded area.
13 Therefore, we cannot say that the treatments are
14 equivalent.
15 So can we begin to also in terms of COX-2
16 agents between to fashion some thoughts about the GI
17 warning? For example, would it require that for
18 removal of the GI warning that we would have
19 equivalence to placebo as would be defined by the
20 sponsor and agreed to by the agency, taking in some of
21 the caveats that I just discussed? Similarly, for
22 major revision, would it require substantial
23 reproducible evidence of in this case endoscopic and
24 clinical outcomes data of superiority over NSAIDS,
25 three as we have selected today, again selected by

1 mutual agreement between the agency and the sponsor?

2 What does the future hold? I think we as

3 well as the sponsor hope the future is bright. But I

4 think what we can say is that the dosing regimens

5 discussed in this NDA regarding treatment of the signs

6 and symptoms of OA may not be effective in other

7 indications. As I have eluded to several times,

8 structural modification in OA and RA may require

9 different doses if that is sought, for example. It

10 was mentioned earlier that this compound has been

11 seeking for prophylaxis of colon cancer and

12 prophylaxis of Alzheimer's disease, and the doses in

13 there may be different.

14 And finally as Dr. Yang has reminded us,

15 we always need to keep an eye out for unique adverse

16 events which are possible with these unique agents.

17 Thank you very much.

18 CHAIRMAN ABRAMSON: Thank you very much.

19 I thank everyone for clarifying many of the issues

20 that have to be addressed this afternoon. I would

21 like now to move into the open public hearing period.

22 I ask each of the people who will present to keep

23 their comments to 7 minutes or less as previously

24 discussed. Our first speaker will be Dr. Palmer of

25 SmithKline Beecham.

1 DR. PALMER: Thank you. Good morning, Mr.
2 Chairman, members of the committee, ladies and
3 gentlemen. My name is Dr. Robert Palmer, and I am
4 from SmithKline Beecham. Last March I presented some
5 philosophical concerns about COX selectivity to this
6 committee. At this time, I would like to make a few
7 additional points bearing on your considerations.
8 Today we have heard a great deal of
9 elegant science and promising information about this
10 drug. I would like to remind you briefly of the
11 hypothesis that has led to such high expectations for
12 it, and then examine the reality behind the
13 hypothesis. This raises the question of what Jim
14 Sheiman has called the "Coxicity of NSAIDS." I will
15 end with reiterating what the standard is now for
16 claiming enhanced or differential safety, particularly
17 as it applies to the GI tract.
18 There has been an enormous amount of
19 interest in the potential advantages of a COX-2
20 specific NSAID. We have heard repeatedly that COX-1
21 is constitutively expressed and is involved in
22 housekeeping functions and that COX-2 is inducible and
23 functions as part of the inflammatory response.
24 Therefore, inhibition of COX-1 should interfere with
25 housekeeping functions and lead to side effects,

1 whereas inhibition of COX-2 should just reduce
2 inflammation. As a result, specific COX-2 inhibition
3 is expected to reduce inflammation without producing
4 side effects.
5 This hypothesis has been embraced widely
6 and has led to high expectations. For example, in a
7 widely read and influential article in The New Yorker,
8 Celecoxib was referred to as superaspirin and
9 described in glowing terms. More than 10,000 patients
10 have received the drug and no side effects have been
11 observed -- none. Now I am sure this is not the
12 position presently, but it certainly is the impression
13 that many people hold.
14 The reality is the situation is much more
15 complicated. COX-1 and COX-2 both have extensive
16 diverse and overlapping functions. It is now widely
17 accepted in scientific circles that both enzymes are
18 expressed constitutively and both are inducible. COX-
19 1 is not just involved in physiological housekeeping.
20 A substantial fraction of the prostaglandins present
21 in inflammation are produced by COX-1. On the other
22 hand, COX-2 is now known to have a number of non-
23 inflammatory physiological roles in the GI tract, in
24 the kidney, and in the reproductive tract and in other
25 organ systems.

1 This brings us to the "Coxicity of
2 NSAIDS." We really don't know the mechanism of the
3 NSAID-induced side effects, nor do we know the extent
4 to which they depend on inhibiting COX-1 and/or COX-2,
5 and inhibiting either enzyme may contribute to side
6 effects, but only rarely will it be the only reason
7 for side effects. Therefore, while a specific COX-2
8 inhibitor may prove to be an excellent product, its
9 pharmacological profile and its side effect profile
10 cannot be inferred reliability from its enzyme
11 specificity, nor will we be able to define the profile
12 from clinical trials in controlled populations. We
13 just don't know yet all we need to know about the
14 functions of these enzymes and their
15 interrelationships with each other and with other
16 important systems.
17 A fundamental assumption of developing a
18 COX-2 specific NSAID is that inhibiting COX-1 is bad.
19 It may sound like heresy, but we should keep in mind
20 the fact that the sky may not in fact fall down if
21 there is some COX-1 inhibition. First of all, it has
22 been shown in certain models of inflammation that
23 specific inhibition of COX-1 leads to as great a
24 decrease in prostaglandin formation as does specific
25 inhibition of COX-2. This inhibition may not be all

1 bad. And in other model systems, it appears to be
2 beneficial. And this may include analgesia, as we
3 have seen here today.
4 Secondly, inhibiting COX-1 does not
5 necessarily lead to side effects. COX-1 knockout mice
6 with more than a 99 percent decrease in COX-1 activity
7 lead quite healthy lives and do not get spontaneous GI
8 lesions. But even though they have no COX-1 to
9 inhibit, they still get gastrointestinal lesions from
10 Indomethacin. So COX-1 inhibition cannot be the
11 explanation for those ulcers. In fact, COX-1 knockout
12 mice are more resistant than wild type mice to the
13 ulcerogenic activity of Indomethacin as well as that
14 of aspirin and of alcohol.
15 Thirdly, inhibiting COX-1 is not
16 necessarily the cause of side effects. Some of the GI
17 side effects of NSAIDS may not be related to COX
18 inhibition at all. These include physicochemical
19 effects on the gastric phospholipid barrier, direct
20 effects on mitochondrial respiration, and importantly,
21 in view of the pre-clinical data just presented,
22 ulcerogenic effects of NSAID glucuronide metabolites
23 on the small intestinal mucosa in mice. For these
24 reasons, one can question whether a COX-2 specific
25 NSAID really has such great theoretical advantages.

1 But theory aside, there are non-selective NSAIDS with
2 excellent safety profiles that are not demonstrably
3 different from the profiles presented here today.
4 On the other hand, inhibition of COX-2 may
5 well be responsible for some of the traditional NSAID
6 side effects. There are a number of areas in which
7 COX-2 plays an important role such that its inhibition
8 may lead to side effects. These areas include healing
9 and repair, particularly ulcer healing, but also other
10 forms of injury and repair. They include
11 gastrointestinal barrier functions. Animals without
12 COX-2 develop peritonitis and septicemia and die.
13 This occurs both when the inhibition is produced
14 genetically, as in COX-2 knockout mice, and when it is
15 as a result of treatment with specific COX-2
16 inhibitors.
17 These areas also include the kidney, and
18 we have heard today that this hypothesis has now been
19 confirmed. Importantly, these areas also include the
20 reproductive functions of ovulation and fertilization
21 and probably perinatal development, and they appear to
22 involve a number of other organ systems, including the
23 vascular system and bone.
24 This slide shows the effect of a strong
25 COX-1 inhibitor, Indomethacin, a specific COX-2

1 inhibitor, and a non-selective COX-1 and COX-2
2 inhibitor at equal molar doses on the glomarial
3 filtration rate in fluid restricted dogs. The point
4 is that both the COX-1 inhibitor and the specific COX-
5 2 inhibitor were capable of affecting kidney function.
6 Thus, it seems likely that specific COX-2
7 inhibitors will be found to share many of the
8 traditional NSAID side effects. In particular, these
9 probably will include delayed ulcer healing and
10 effects on renal sodium homeostasis. In addition,
11 there is the theoretical question to what happens with
12 unopposed inhibition of one COX enzyme. You just saw
13 an example of this in the dog, where inhibition of
14 either COX-1 or COX-2, but not both COX-1 and COX-2
15 altered renal function. I should note that there may
16 be other explanations than enzyme specificity for
17 those differences.
18 In tissues such as the lung, unopposed
19 COX-2 inhibition also may have unanticipated effects.
20 If it does, it is likely that such events will not
21 show up in clinical trials. They may only show up in
22 special at-risk populations. What are the practical
23 implications of these issues?
24 CHAIRMAN ABRAMSON: Dr. Palmer?
25 DR. PALMER: Yes.

1 CHAIRMAN ABRAMSON: Can you come to a
2 conclusion, please?
3 DR. PALMER: Yes. Can I go to the last
4 slide then, please? I would just like to say in
5 conclusion that these considerations are not -- never
6 mind. Turn it off. These considerations are not
7 meant to imply that specific COX-2 inhibitors may not
8 be good drugs. They may well be excellent drugs. I
9 would simply emphasize the three points. That the
10 roles of COX-1 and COX-2 are complex and incompletely
11 understood. The safety profile of an NSAID cannot be
12 assumed from its enzymatic specificity. And the same
13 rules for demonstrating a superior safety profile
14 apply to all NSAIDS, that is, large adequately powered
15 outcome studies are necessary. Thank you for the
16 opportunity to make these remarks.
17 CHAIRMAN ABRAMSON: Thank you. May I ask
18 you one question -- a Chairman's prerogative. Are you
19 willing to go so far and say that the inhibition of
20 COX-1 is not the cause of gastric ulcers?
21 DR. PALMER: I don't know, but I know it
22 is not a sufficient cause.
23 CHAIRMAN ABRAMSON: Okay.
24 DR. PALMER: How much it contributes is
25 anybody's guess.

1 CHAIRMAN ABRAMSON: Okay. Thank you.
2 Next is Dr. Cooper of Whitehall Robbins. Okay, Dr.
3 Soller, Non-prescription Drugs Manufacturing
4 Association.
5 DR. SOLLER: Thank you, Dr. Abramson,
6 members of the committee, FDA. I am Dr. Bill Soller,
7 Senior Vice President and Director of Science and
8 Technology for the Non-prescription Drug Manufacturers
9 Association, a 117-year-old trade organization
10 representing the manufacturers and distributors of
11 non-prescription medicines and dietary supplements.
12 Our members represent over 95 percent of
13 the OTC marketplace, including all of the major
14 national brands and store brands or generic OTC
15 analgesic antipruritic products. Happily, I don't
16 have a slide projector and have to deal with what Dr.
17 Palmer dealt with.
18 Few OTC categories have as extensive a
19 history of safe and effective use according to label
20 directions as OTC analgesics, with billions of tablets
21 and liquid dosage units consumed annually in the
22 United States. With the introduction of any new drug
23 into a class of drugs, companies often seek to develop
24 distinctions among the competing treatments. And how
25 these distinctions are developed is extremely

1 important to avoid unfair disparagement among
2 currently marketed products. On one level, if the
3 distinctions are not accurate reflections of the data,
4 they are scientifically unsound. And on another
5 level, if they are unscientifically based
6 distinctions, they may mislead and confuse consumers.
7 In the case of the COX-2 inhibitors, we asked that the
8 advisory committee cast its recommendations in the
9 context of the safety of these ingredients, and the
10 one that you are looking at today, in the context of
11 the dosages, the durations of use, the nature and the
12 severity of the conditions of use, the limitations in
13 terms of extrapolating from clinical data where
14 patient selection is tightly screened to the much
15 broader OTC in-use situation and also in the context
16 of the limited comparative data that you have on OTC
17 analgesics. Our reason is to avoid the blurring of
18 the comparative safety of the COX-2 inhibitors with
19 OTC analgesics as your recommendations will be picked
20 up by the media, and trust me they will.
21 To elaborate briefly, it is important that
22 the conclusions on clinical data from a prescription
23 COX-2 inhibitor used at relatively higher doses for
24 longer durations for chronic more severe conditions
25 are not unfairly commingled on a comparative basis

1 with data from OTC analgesics, where self-care for
2 pain relief is done at lower doses for acute, less
3 severe, self-treatable OTC conditions such as tension
4 headache, the general aches and pains of the common
5 cold, and so forth.
6 Now that is not to say that there aren't
7 individuals that may be sensitive to one or another
8 OTC analgesic. That is true of any drug. But the
9 extensive market history as well as the very favorable
10 adverse experience profile for OTC analgesics at
11 recommended dosage supports the conclusion that they
12 are safe and effective for self-treatment.
13 Now additionally, OTC's in general are
14 widely regarded as an effective approach to limiting
15 escalating healthcare costs. They have earned this
16 distinction by virtue of their favorable market
17 profiles and in terms of their clinical experience
18 often shown prior to their OTC availability. And as
19 a result, it is important that a balanced message in
20 the drug review environment is created so that the
21 known significant contributions of currently marketed
22 OTC analgesic anti-pruritics to the healthcare cost
23 equation are not lost as a result of consumers
24 needlessly becoming patients and seeking Rx therapies
25 at higher cost to the healthcare system.

1 In summary, as with any drug, our concern
2 is not with what we know. Our concern is what we may
3 not know until substantial post-marketing experience
4 is available. We ask the committee to be sure its
5 recommendation is made in such a way as to limit your
6 recommendations from being misinterpreted, and to the
7 media covering this, we -- and thinking back to Dr.
8 Witter's quote from the Wall Street Journal and Dr.
9 Palmer's quote from The New Yorker, we ask that you
10 also take on the mantle of responsibility to ensure
11 the data are not misrepresented to your readers.
12 Because consumers can confidently use OTC analgesics
13 according to label directions for a wide variety of
14 self-treatable conditions. Thank you very much.
15 CHAIRMAN ABRAMSON: Thank you. Dr. Liang?
16 DR. LIANG: I have a question. Are there
17 systematic active surveillance studies of OTC
18 analgesics and NSAIDS?
19 DR. SOLLER: Yes, there are.
20 DR. LIANG: Could you give me some?
21 DR. SOLLER: Absolutely. Those products
22 that are covered under new drug applications have the
23 same active surveillance procedures that prescription
24 products would have in terms of the NDA and post-
25 marketing reporting requirements from the standpoint

1 of the analgesics that are covered under the OTC
2 review and the monograph system. And having been in
3 the industry for some 20 years at the Association
4 since 1985, we have done many post-marketing adverse
5 experience compilations for FDA, and I know that the
6 companies that represent the vast exposure in any one
7 category of OTC's, whether it is analgesics or not,
8 are using state of the art post-marketing surveillance
9 capture systems.
10 CHAIRMAN ABRAMSON: Okay. Thank you very
11 much. The next individual is Dr. Bryant from the Bayer
12 Corporation.
13 DR. BRYANT: No, from the Aspirin
14 Foundation. I am Tom Bryant. I am a physician and I
15 am President of the Aspirin Foundation of America,
16 which is an organization dedicated to the safe and
17 effective use of aspirin. I appreciate the
18 opportunity you have afforded the foundation to make
19 a very brief statement.
20 Arthritis affects 37 million people in the
21 United States and is a major cause of disability. As
22 a disease entity, it has enormous personal and
23 societal impact and has led many pharmaceutical firms
24 to seek new treatment modalities. The Aspirin
25 Foundation applauds those firms that have invested the

1 time and the resources into new approaches to the
2 management of crippling arthritis such as we heard
3 this morning. It must be kept in mind through your
4 deliberations today that there are a variety of
5 therapeutic agents currently available to treat this
6 disease, and many have a long history of safe and
7 effective use. Aspirin, for instance, has been
8 marketed for 100 years and has been the gold standard
9 by which all new agents have been compared for years.
10 In fact, as the COX-2 agents have been developed, many
11 have suggested that they be referred to, as we saw in
12 the slides, superaspirin. Unfortunately, this implies
13 that they are superior to aspirin in all aspects.
14 The AFA believes that this is neither
15 appropriate nor acceptable. Each of the agents
16 currently available has unique properties. It is the
17 aggregate of their pharmacology, kinetics and dynamics
18 that define their effectiveness and tolerance. The
19 new COX-2 inhibitors offer neither the history of safe
20 use nor the additional cardiovascular benefits that
21 aspirin offers.
22 As your deliberations unfold today
23 relative to the safety and effectiveness of the one
24 drug, it is important that you consider this agent on
25 its own merits and not compare it solely and simply to

1 existing therapies. Current therapies have stood the
2 test of time and represent an important place in the
3 therapeutic armamentarium of arthritic care, not to
4 mention the economic and access benefits afforded by
5 over-the-counter medications as referred to by Dr.
6 Soller. In addition, claims of superiority negate the
7 benefits that might be accrued from a physician's
8 recommended use of aspirin for cardiovascular disease
9 management.
10 Lastly, in the interest of gaining media
11 attention for new therapies, manufacturers have
12 sometimes highlighted concerns with current NSAIDS,
13 including quite often aspirin. These concerns are
14 often frightening to the consuming public and are
15 likely to lead users to believe that the benefit to
16 risk ratio from available products is not acceptable.
17 This is not true and should not be condoned by this
18 review or an FDA approval. Whatever your thoughts are
19 regarding aspirin and the other currently available
20 NSAIDS, comparative claims should be validated by
21 meaningful data from scientifically rigorous studies.
22 We implore you to focus today's review on the weight
23 of evidence in support of this drug talked about this
24 morning and resist the temptation to base the
25 deliberations solely on comparative safety. Thanks

1 very much for this opportunity.

2 CHAIRMAN ABRAMSON: Okay. Thank you.

3 There will be a discussion this afternoon about the

4 use of aspirin and the COX-2 inhibitors. So I think

5 that will come back before us. The final speaker is

6 Dr. Sidney Wolfe, Director of Public Citizens Health

7 Research Group.

8 DR. WOLFE: Thank you. A paramount issue

9 to the public safety is whether NSAIDS that are

10 promoted as preferential, selective or specific

11 inhibitors of the enzyme COX-2 seeking to

12 differentiate themselves in a crowded marketplace from

13 other NSAIDS can be labeled as having less toxicity,

14 particularly GI toxicity.

15 Not frequently discussed is that COX-2 may

16 have other important physiological functions in

17 addition to its role in inflammation, such as GI tract

18 tissue repair, epithelial integrity, renal vascular

19 homeostasis, fetal renal development during pregnancy

20 -- this is the COX-2 knockout animal in which the

21 kidney does not develop properly in the absence of

22 COX-2 -- ovarian function and fertility and cartilage

23 repair. Purported new classes of drugs such as

24 Celecoxib offer not only new mechanisms of action, but

25 also new mechanisms of potential toxicity and the

1 possibility of a new spectrum of adverse effects.

2 Several weeks ago, November 12, 1998, the

3 headline of a PR news wire story citing Monsanto as a

4 source referred to Phase III studies on Celecoxib "as

5 effective as Naproxen and Diclofenac but with a

6 gastrointestinal safety profile similar to placebo."

7 The text referred to a paper presented at the American

8 College of Rheumatology meeting and described studies

9 using upper GI endoscopic exams which show that the

10 incidence of gastroduodenal ulcers in patients given

11 Celecoxib was "four times lower" than patients taking

12 Diclofenac. This finding is consistent with that of

13 former advisory committee member here, Dr. Lee Simon,

14 and his colleagues. Dr. Simon in his own Phase II

15 endoscopy trial found it "indistinguishable from

16 placebo" in terms of the amount of ulcers. But Simon

17 went on to warn, however, that "although this model is

18 sensitive to acute mucosal effects, the results do not

19 necessarily correlate with clinical events such as

20 bleeding, perforation or obstruction and that only

21 larger trials evaluating long-term outcome and higher

22 dosage levels will fully define the GI effects of

23 selected COX-2 inhibitors." A quite similar good news

24 story were the early results on another selective COX-

25 2 inhibitor, Miloxicam, marketed in the UK since

1 September of 1996. A study of healthy people given
2 Miloxicam or placebo or Peroxicam for 28 days found
3 that using endoscopy again, "no significant mucosal
4 damage" occurred in either the placebo or the
5 Miloxicam group. But recently the British Government
6 required a major increase in the warnings on this drug
7 because of severe gastrointestinal adverse effects.
8 In the August 1998 *Current Problems in Pharmaco-*
9 *Vigilance*, the British Medicines Control Agency and
10 the Committee on Safety in Medicine reported on the
11 first one year and nine months of marketing experience
12 of Berendt-Engelheim's Miloxicam. Of a total of 1,339
13 adverse reactions reported to the government for the
14 drug, 41 percent or 549 were GI adverse effects with
15 18 percent of these or 99 being reports of
16 perforations, ulcers or bleeding, including 5 deaths.
17 *The Drug and Therapeutics Bulletin*, the British
18 equivalent of *The Medical Letter*, but sent to all
19 physicians in Britain, said "there is no convincing
20 evidence that the risk of the severest adverse
21 gastrointestinal events; namely, peptic ulceration,
22 perforation and bleeding, is lower with Miloxicam than
23 with other NSAIDS when given at equally effective
24 doses. Miloxicam has not been compared with
25 Ibuprofen, which comes out best in most safety

1 assessments."

2 As this committee well knows, despite
3 apparently large differences between the more
4 traditional COX-1 inhibiting NSAIDS as far as the
5 occurrence of perforations, ulcers and GI bleeding --
6 and in the presentation here we have a chart that we
7 presented in December of 1994 -- the FDA decided on
8 identical class labeling for all these older NSAIDS,
9 and this includes differences between Ibuprofen and
10 Peroxicam at the extremes of 5 to 10-fold in some
11 cases.

12 So on one hand showing huge differences in
13 GI toxicity from case control studies to be sure
14 between Peroxicam on one end and Ibuprofen still did
15 not prevent a class labeling. There needs to be clear
16 evidence from comparative long-term higher dose
17 randomized trials in which Celecoxib or any other COX-
18 2 type of anti-inflammatory drug is compared to the
19 least dangerous of these older drugs such as Ibuprofen
20 that there is a statistically significant lower amount
21 of serious GI complications, such as perforations,
22 ulcers or bleeding with the COX-2 inhibitor drug.
23 Unless this evidence is produced, there is no more
24 reason, according to the logic of this committee, to
25 spare any COX-2 inhibitor from the class label now

1 applied to all of the other NSAIDS than there is to
2 distinguish between the members of this older class.
3 The question, among others, is will this committee and
4 the FDA require that such studies be finished before
5 subjecting millions of American arthritis patients,
6 under the unproven assumption that this and similar
7 drugs are much safer in terms of serious adverse
8 effects, to treatments which, like Miloxicam turn out
9 to be more dangerous than originally thought.
10 There is a table in here which simply
11 points out that the tight relationship that people
12 would like to believe between the ratio of COX-1 to
13 COX-2 as presented by Searle, or COX-2 to COX-1 as
14 other people present, doesn't necessarily correlate.
15 Ibuprofen from observational studies is generally
16 recognized as having the least GI toxicity in clinical
17 practice. It has a low TI of 1.13, but a COX-2/1
18 ratio of 15, indicating this NSAID is predominantly a
19 COX-1 inhibitor. This is an observation that is in
20 direct contradiction that drugs with the greatest COX-
21 2 selectivity should be the NSAIDS with the least GI
22 toxicity.
23 SmithKline, who made a presentation just
24 before, called Relafen/Nabumetone preferential COX-2
25 inhibitor. However, FDA found SmithKline Beecham in

1 violation of the Food, Drug and Cosmetic Act on two
2 occasions for the false and misleading advertising
3 that because Nabumatone is a preferential COX-2
4 inhibitor it was safer than other NSAIDS. The company
5 is required to send a letter to health professionals
6 saying it has no valid data to support their claim
7 that Nabumatone was less toxic to the GI tract, was
8 safer for the kidneys, and caused less bleeding
9 problems than other NSAIDS.
10 In closing, I would just like to commend
11 the FDA on its presentation covering some points that
12 didn't get necessarily made in the company's
13 presentation and believe that this committee will take
14 very seriously all that they have heard. And again,
15 the issue as put to Dr. Witter is not whether or not
16 the drug gets approved. It clearly has efficacy at
17 least for RA and OA, if not for acute pain, but
18 whether -- and the main issue is whether the class
19 labeling now existing for NSAIDS can be dropped. We
20 would argue strongly that there is no scientific
21 basis, particularly considering the most serious
22 adverse GI effects, for dropping the labeling. The
23 idea of doing a post-marketing study makes sense, but
24 it only makes sense with the marketing being the same
25 in terms of GI toxicity information to doctors or

1 patients as is for the other NSAIDS. Thank you.

2 CHAIRMAN ABRAMSON: Thank you very much.

3 Okay, I thank everyone. We will reconvene at 1:30.

4 Thank you very much.

5 (Whereupon, at 12:28 p.m., the meeting was

6 adjourned for lunch to reconvene at 1:33 p.m.)

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

2 (1:33 p.m.)

3 ACTING CHAIR ABRAMSON: We're going to

4 begin.

5 There was a great deal of interesting

6 information presented this morning and I'm sure many

7 people have questions that they would like ask,

8 particularly among the panel, for clarification. But

9 I think because we'd like to focus -- the FDA has

10 given us a series of questions that they would like,

11 11 questions, that they would like the panel to

12 address. And I think that if the panel goes through

13 each of the questions, the discussion that comes will

14 leave opportunity for people to ask questions of

15 presenters from this morning to help address the

16 specific FDA issues.

17 So we will begin with Question Number 1

18 which is: Should Celecoxib be approved for the

19 indications of the treatment of the signs and symptoms

20 of osteoarthritis and rheumatoid arthritis?

21 And why don't we just address

22 osteoarthritis first just to keep things clear. Any

23 member of the panel like to comment on that?

24 Is there anyone who wasn't satisfied that

25 the data showed efficacy in osteoarthritis?

1 DOCTOR TILLEY: I just had a general
2 technical question. I know that both the FDA and the
3 Searle used last-observation-carried-forward as your
4 way of dealing with missing data. And I just wondered
5 why that approach was chosen, what the rationale was
6 for that?
7 DOCTOR NEEDLEMAN: Shall we give a
8 statistical answer? Let me -- Does the FDA want to
9 respond -- say something first and then we could bring
10 our statistician forward.
11 ACTING CHAIR ABRAMSON: We can't hear you.
12 MS. REEDY: Microphone.
13 DOCTOR HYDE: Apparently that's what's
14 been done traditionally looking at these things. Part
15 of the reason is that patients by and large achieve a
16 steady state so that extrapolation --
17 ACTING CHAIR ABRAMSON: We're sorry. We
18 can't hear anything.
19 DOCTOR HYDE: Is that working?
20 Apparently that's what's been done
21 historically at these trials and the idea being that
22 flaring patients by and large are pretty much at
23 steady state after it subsides. So it's been sort of
24 a poor man's version of a better statistical analysis
25 you could do. But that's what we've looked at before.

1 In other situations, like the analgesic
2 trials we don't like to do it that way particularly.
3 Since patients are fairly constant anyway, that's the
4 approach that has been used.
5 DOCTOR TILLEY: Would you want to comment
6 on the --
7 DOCTOR NEEDLEMAN: I'm sorry. Could you
8 repeat what he said? What Doctor Hyde said. We just
9 couldn't hear him.
10 DOCTOR TILLEY: Well, his answer was it's
11 always been done that way, and I guess I'd like a
12 little more rationale then from those who have always
13 been doing it that way as to why.
14 DOCTOR ZHAO: I guess that's so much the
15 reason. And it was stated in the protocol and it was
16 discussed with FDA and a lot of applications also use
17 that method. Recently there have been discussions
18 using a different approach but we tried it on the
19 approach -- the conclusion is not changed.
20 DOCTOR TILLEY: Using different approaches
21 to replacing the missing values did not -- your data
22 was -- your analysis was robust to those differences?
23 DOCTOR ZHAO: They are different
24 theoretical approaches. What we did was we also used
25 the GE model to look at longitudinal data with and

1 without last observation carried forward the result
2 looked the same.
3 DOCTOR TILLEY: What about for the
4 outcomes that are binary like for rheumatoid
5 arthritis, the ACS 20 -- I mean ACR 20 where in some
6 analyses I've seen in other studies, one would
7 classify a person as a failure to respond if they
8 dropped out rather than giving them the last
9 observation carried forward.
10 Did you look at any of those kinds of
11 analyses?
12 DOCTOR ZHAO: We did not. We only looked
13 at the continuous variable.
14 DOCTOR TILLEY: What about the FDA? Did
15 you look at anything like that?
16 DOCTOR LU: Yes. As the statistical
17 reviewer for RA trial, I did the analysis which I
18 treat any drop -- early drop-outs as a failure. And
19 then I only use the completers to -- as a condition to
20 classify success. So anybody who drops out before,
21 say, week 12 will be classified as a failure. So, in
22 this way still are the sponsor's results are similar
23 statistically wise to the responder's results.
24 ACTING CHAIR ABRAMSON: Fine. Are there
25 any other comments from the panel about

1 osteoarthritis?

2 Can I have a show of hands for those --

3 let's just vote on the osteoarthritis piece. All

4 those who think that Celecoxib should be approved for

5 osteoarthritis raise their hand.

6 (Whereupon, a show of hands.)

7 ACTING CHAIR ABRAMSON: All those opposed.

8 (Whereupon, a show of hands.)

9 ACTING CHAIR ABRAMSON: Eight to one.

10 Doctor Fernandez-Madrid, would you like to

11 comment on your thinking?

12 DOCTOR FERNANDEZ-MADRID: What I'm

13 thinking is is I think the studies that were shown on

14 the models that were shown showed efficacy. But, I'm

15 not really convinced that this reflects the real

16 world. That is, I was not given a good explanation on

17 the selection of the patients, on the diagnostic

18 criteria. I'm sure that these exist, and I was

19 talking with Roland Moskowitz, and he assures me that

20 these exist.

21 DOCTOR NEEDLEMAN: May we, in fact,

22 address that, because we didn't have a chance to --

23 DOCTOR FERNANDEZ-MADRID: I would like to

24 address that.

25 DOCTOR NEEDLEMAN: Yes, may we call Rollie

1 Moskowitz, please?

2 ACTING CHAIR ABRAMSON: Yes, that's fine.

3 I think -- Let's have more discussion on this point.

4 DOCTOR MOSKOWITZ: Thank you, Doctor

5 Abramson. I'm Doctor Roland Moskowitz, Professor of

6 Medicine at Case-Western Reserve University School of

7 Medicine and Director of the Division of Rheumatic

8 Diseases at University Hospitals of Cleveland.

9 I think it's a very important question

10 that you asked Fernandez-Madrid. The criteria for

11 entry into the study, into the protocol, was the

12 definition of osteoarthritis of the knee or

13 osteoarthritis of the hip by American College of

14 Rheumatology criteria. In other words, for the knee,

15 they had to have a history of pain or more days than

16 not in the preceding month for a specific duration,

17 plus osteophyte formation on X-ray. In addition, they

18 had to have one of three criteria clinically and that

19 is that they be age over 45 to 50 which is accepted

20 for the criteria, crepitance and morning stiffness

21 less than 30 minutes. They all fulfilled this

22 criteria in order to enter this study.

23 For hip osteoarthritis to get into the

24 study, each patient had to satisfy the ACR criteria,

25 the American College of Rheumatology criteria, of hip

1 X-ray changes showing joint space narrowing,
2 osteophyte formation, and a sedimentation rate of less
3 than 20 millimeters per hour. All fulfilled this
4 criteria.
5 In addition, it wasn't -- Now, that meant,
6 Doctor Fernandez-Madrid, that they had to satisfy at
7 least Stage II criteria of the Kelligran-Lawrence*
8 criteria. And they all had to have definite
9 osteoarthritis.
10 And now, no one was allowed in the study
11 who had a functional classification of grade 4. In
12 other words, they couldn't be severely disabled or
13 crippled by their disease. They also had to have a
14 minimum level of disease activity or symptomatology in
15 order to get into the study. And that is, on a visual
16 analog scale for pain in the previous 24 hours, they
17 had to have 40 millimeters or more, which is
18 significantly higher than most studies which allow
19 entry at 30 millimeters or more. They also had to
20 have pain on a patient global that was rated as very
21 poor or poor, patient on a physician global of very
22 poor or poor, and an elevated osteoarthritis severity
23 index.
24 Then, all patients were then randomized to
25 the two different groups; and, as it turned out, the

1 baseline randomization was very powerful and there was
2 a minimal difference in terms of the onset baseline
3 data for all these individuals.
4 Does that address the question?
5 DOCTOR FERNANDEZ-MADRID: This is what I
6 wanted to hear. I withdraw my negative vote.
7 ACTING CHAIR ABRAMSON: And I apologize to
8 Doctor Geis. I guess that was on the one slide we
9 didn't get to show.
10 DOCTOR NEEDLEMAN: So may we show the next
11 3,000?
12 ACTING CHAIR ABRAMSON: Rheumatoid
13 arthritis. Anyone have any discussion or comments or
14 questions about the data of efficacy in the treatment
15 of rheumatoid arthritis?
16 DOCTOR FERNANDEZ-MADRID: I think efficacy
17 has been shown and I think I was satisfied with that.
18 However, it may not reflect, again, what happens in
19 the real world. And I think nobody uses nonsteroidals
20 alone the treatment of rheumatoid arthritis anymore.
21 I think I haven't seen any of these patients for years
22 now.
23 And I think one would like to look at the
24 treatment of rheumatoid arthritis with a new drug in
25 the context what is being done in rheumatoid arthritis

1 which is a combination of therapy, new second line
2 drugs, and so forth. I think this is what I would
3 like to see for a new drug that is introduced in the
4 treatment of rheumatoid arthritis.
5 Also, in the treatment of rheumatoid -- in
6 the trial that we're comparing with methotrexate, I
7 think it would be good to know what dose of
8 methotrexate were used at that time for the patients
9 that were treated for rheumatoid arthritis and how did
10 the ALT and noracrinphosphotase do phase 2 after six
11 months of treatment.
12 ACTING CHAIR ABRAMSON: Can we address
13 some of those issues?
14 DOCTOR NEEDLEMAN: Yes, we --
15 ACTING CHAIR ABRAMSON: -- methotrexate
16 dose and prednisone dose, also?
17 DOCTOR NEEDLEMAN: Yes, I think I'll call
18 Steve Geis. We have rheumatoid patients at
19 methotrexate and steroids, and we followed them very
20 closely.
21 DOCTOR GEIS: So just to review at
22 baseline, the patients were similar across the
23 treatment groups in terms of the status of the
24 rheumatoid arthritis and what other medications they
25 were taking for their rheumatoid arthritis.

1 And if I could have the slide, please, we
2 can show you that baseline status.
3 Here, we show that we allowed patients who
4 were using corticosteroids, methotrexate or DMARDs.
5 And this shows the percent of the patients who were on
6 any one of these other agents for treating of
7 rheumatoid arthritis.
8 Overall, across all treatment groups, and
9 in both studies, about 70 percent of patients were on
10 some other medication for controlling their rheumatoid
11 arthritis. So in terms of methotrexate, the dose was
12 about 25 milligrams per week was the dose that
13 patients had been on. And this was maintained through
14 the course of this study.
15 DOCTOR NEEDLEMAN: We should also remind
16 you that Doctor Aziz Karim then presented that data,
17 that there was no pharmacokinetic interference with
18 the methotrexate blood levels in the face of Celecoxib
19 treatment.
20 Doctor Strand, do you have a comment that
21 you might like to add to this?
22 DOCTOR STRAND: I have very little to add
23 except to say that the patients were on standard
24 background therapies, they had their non-steroidal
25 therapy withdrawn over a week to two weeks and that

1 they tended to also have a flare of their disease
2 during that time after which they were started on one
3 of the treatment groups.
4 In general, the demographics of the RA
5 population reflects demographics that we've seen in
6 the last several months with various trials of RA
7 patients as well as fairly early to fairly long-
8 standing disease.
9 ACTING CHAIR ABRAMSON: Just to follow up
10 on Doctor Fernandez-Madrid's question. In theory, you
11 might be able to lower steroid dose if you could add
12 an NSAID so that it didn't contribute to
13 ulcergenicity. Did you look at steroid dose over time
14 to see whether in fact were people allowed to take
15 with their steroids?
16 DOCTOR STRAND: The steroid dose was held
17 constant during the studies. And again, these were
18 relatively short-term studies. Two of them were 12
19 weeks and one of them was six months. So, one would
20 probably not expect to start doing that kind of
21 steroid tapering in such a short period of time.
22 ACTING CHAIR ABRAMSON: Ms. Malone.
23 MS. MALONE: I just wondered how high were
24 the steroids? What level were they at?
25 DOCTOR STRAND: They were allowed no more

1 than the equivalent of 10 milligrams of prednisone a
2 day.
3 ACTING CHAIR ABRAMSON: Doctor Liang.
4 DOCTOR LIANG: Did you really mean 25
5 milligrams of methotrexate on average?
6 DOCTOR STRAND: They were allowed up to 25
7 milligrams. I would say that the average dose was
8 probably a little bit lower. That was the maximum.
9 They were restricted to PO. No IM.
10 ACTING CHAIR ABRAMSON: Thank you.
11 Any other questions from the panel?
12 I think I'd like to take a vote on this
13 issue unless someone has any last minute concerns.
14 All those in favor of answering yes to the
15 first question on rheumatoid arthritis, that Celecoxib
16 be approved for treatment of RA, please so signify.
17 (Whereupon, a show of hands.)
18 ACTING CHAIR ABRAMSON: All those opposed.
19 (Whereupon, a show of hands.)
20 ACTING CHAIR ABRAMSON: Thank you.
21 The next question is number 2 which has to
22 do with the -- Oh, I'm sorry.
23 AUDIENCE MEMBER: What was the count, I
24 think people are asking?
25 ACTING CHAIR ABRAMSON: 9-0. I'm sorry.

1 I assume those were physicians or
2 scientists back there who wanted to know.
3 DOCTOR NEEDLEMAN: If I could have put my
4 mother back there, I would have.
5 ACTING CHAIR ABRAMSON: All right. For
6 the management of acute pain, the division's usual
7 requirement is replicated evidence of efficacy in two
8 different pain models. Do the people have these
9 questions or should I -- So, question 2, and people
10 just look at it for a minute. And I guess the
11 recommendation of the agency was that the usual
12 criteria for approval for pain management was not met
13 based on the NDA.
14 So I would like to open this piece to
15 questions from the committee.
16 I just had a question about analgesia
17 versus anti-inflammation. And with traditional
18 NSAIDs, as we all know, is that at lower doses they
19 have analgesia and you don't really get anti-
20 inflammation until you raise the dose. Do you see
21 that kind of activity with the COX-2 drugs, that is,
22 you can't treat your inflammatory models but you do
23 get analgesic responses?
24 DOCTOR NEEDLEMAN: I'm not sure of the
25 question. You're asking a pre-clinical or asking a

1 clinical question?

2 ACTING CHAIR ABRAMSON: I don't know if

3 you've looked at it clinically. I guess it's a pre-

4 clinical question, unless you have data clinically.

5 DOCTOR NEEDLEMAN: The reality is, all the

6 animal models of pain require use of things like

7 carrageen which induce, in fact, inflammation. So,

8 there is no -- and we don't have any neurological pain

9 models. So by and large, there is an underlying

10 inflammatory response.

11 ACTING CHAIR ABRAMSON: I guess the

12 question to the FDA staff, are there precedents where

13 you've approved pain indications in the absence of the

14 things that you reported to us are the usual

15 requirements for pain indication?

16 DOCTOR HYDE: Not in memory at least. I

17 mean, there are other combinations. For example,

18 dysmenorrhea might be a second model rather than the

19 post-surgical. But generally, in order to get sort of

20 a general pain indication, the philosophy has been at

21 least more than one particular model should be

22 investigated.

23 Now, the post-general and post-surgical

24 are not all that different. But in fact, they do have

25 different characteristics as far as the relative

1 performance of, say, NSAID and narcotics. So, there
2 is some difference in that model.
3 There was a question earlier about
4 specific types of pain. In fact, dysmenorrhea is
5 recognized. If that is one of the models that is
6 included, that is listed as a specific indication.
7 Also, as the committee's discussed in the
8 spring when you brought up some of the pain claims,
9 the neuropathic pain maybe would be something
10 different which would merit specific mention in
11 labeling. But other than that, we haven't for use in
12 dental pain, or for use in post-surgical, that hasn't
13 been the approach that was being used.
14 DOCTOR NEEDLEMAN: May I request of the
15 committee, we feel rather strongly about the issue of
16 pain and the multi-dose treatment, and the short term
17 pain and would actually like to make a presentation of
18 some of the data that really looks at OA flare in the
19 context of pain as a bona fide second -- as a second
20 model because it was so much of an issue this morning
21 and now. And if you agree to that, I think I'd like
22 to start by calling on Roland Moskowitz to give the
23 data and the support to that.
24 DOCTOR DELAP: If I could just add a
25 couple of comments.

1 ACTING CHAIR ABRAMSON: Sure.

2 DOCTOR DELAP: First, about the pain
3 models. Again what we're really looking for, I think,
4 with the acute pain is the concept of when people have
5 some kind of acute pain that is not self-limited
6 typically to six or eight hours as dental pain may be,
7 what are the performance characteristics of the
8 product?

9 In other words, you have someone who has
10 pain that lasts for a day or two days but it's still
11 under the general rubric of acute pain, how long does
12 the relief last from the dose and what's the dosing,
13 what's the proper dose, and understanding some of
14 these issues about what's the analgesic dose versus
15 the anti-inflammatory dose.

16 So, that's some of the underlying
17 rationale behind looking for what we call a single-
18 dose or a couple-dose acute pain model as in dental
19 pain versus a multiple-dose acute pain model as in
20 post-op or dysmenorrhea. And then we tend to look,
21 historically at least, at the things like OA flare as
22 being more of a -- perhaps an acute manifestation with
23 a chronic pain issue more reliant on the anti-
24 inflammatory features of the product perhaps.

25 So, those are some of the distinctions

1 we've drawn. And again, what we're really looking at
2 here is how you dose the product for an acute pain
3 episode. What's the patient's expectation that their
4 pain is going to be relieved. How often might they
5 have to take the medication. What's the proper dose.
6 And that's why we've drawn the distinction, at least
7 historically, between the acute pain models and the
8 more chronic illnesses like OA and RA.
9 Now, that's not to say that you could not
10 use OA as, perhaps, OA flared, as perhaps the acute
11 pain model. But we'd really want to see it studied as
12 an acute pain model where you have a lot of
13 observations over the first couple of days to really
14 get a good understanding of the kinds of the analgesic
15 effects in the first couple of days in the repeated
16 dosing. And again, what's the proper dose to get kind
17 of the analgesic effect acutely as opposed to the
18 anti-inflammatory result.
19 Doctor Moskowitz.
20 DOCTOR MOSKOWITZ: Thank you, again,
21 Doctor Abramson.
22 Doctor Liang, I appreciate your comments
23 and hope that we can address those to satisfaction.
24 I respectfully would like to submit that
25 osteoarthritis is an appropriate model for evaluation

1 of a short-term multiple dose pain model which is --
2 and I think the guidelines which Doctor Sunshine will
3 address shortly following my presentation relate to
4 using different models, not only acute pain but short
5 term multiple dose models. And hopefully we can
6 demonstrate this.
7 One of the things in using osteoarthritis
8 as a model is using it for pain. We're not looking at
9 osteoarthritis as a disease when we're doing these
10 kinds of administration of agents. Pain is the
11 primary outcome manifestation of osteoarthritis. I
12 mean, there's no study that one does -- you can do
13 function but every primary study is done using pain as
14 an outcome.
15 Now, it's not a new concept. Using
16 osteoarthritis as a pain model is not a new concept.
17 There is precedent for this in the literature, and
18 actually, if I'm not mistaken, OxyContin and Tramadol
19 utilized osteoarthritis patients in approval for pain
20 for acute pain manifestations.
21 And, if I can have slide 450, please.
22 These are just a short list of studies in
23 which analgesics without anti-inflammatory effects, as
24 Doctor Abramson mentioned, and we'll bring that
25 question in a little bit, Doctor Abramson, in terms of

1 evaluating this.

2 Analgesic study for the pain of
3 osteoarthritis, not for osteoarthritis as a disease
4 but osteoarthritis as a pain model. Acetaminophen
5 study by Doctors John Bradley and Kenneth Brandt,
6 Tramadol study by Doctor Sanford Roth, OxyContin
7 study, Sanford Roth, Codeine and paracetamol which is
8 a combination of pentazocine, or Talwin,
9 dextropropoxiphine, and diodal codeine. And as I
10 mentioned, there are additional ones that have been
11 studied purely as an analgesic agent.

12 Thirdly, the question comes up -- can we
13 have the slide off please -- in looking at this as
14 pain, can we look at osteoarthritis as pain rather
15 than as a disease? If you study osteoarthritis as a
16 disease, it's required that you have, at least in most
17 studies, three major outcomes that you study. One is
18 pain. One is function. And one is patient global.
19 In addition to secondary parameters.

20 On the other -- and if you do that kind of
21 study, it's, if not required, it's highly recommended
22 by everyone who does these studies and I think the FDA
23 agrees with this and has been part of these
24 discussions, that you use a single signal joint. In
25 other words, you use knee for everybody in the study

1 or you use hip for everybody in the study. Because
2 knee OA, may not be the same as hip OA, may not be the
3 same as hand OA.
4 On the other hand, if you're doing a study
5 looking at OA as a pain model, you -- it's common
6 practice in studies, certainly in the literature, to
7 use patients whose primary signal joint is the knee,
8 some patients whose primary signal joint is the hip,
9 and even spine. So, you can have hip, knee, and
10 spine, hip and knee, demonstrating the universality of
11 pain as the item that you're testing, as the outcome
12 item, which is being tested in that situation. So,
13 you're looking at, once again, osteoarthritis as a
14 pain model.
15 This translates into clinical
16 applicability. For example, I mentioned the study by
17 Doctors Kenneth Brandt and John Bradley who looked at
18 comparing acetaminophen as a treatment for
19 osteoarthritis, a pure simple analgesic as compared to
20 analgesic doses of non-steroidals ibuprofen at 1,200
21 milligrams a day versus 2,400 milligrams a day an
22 anti-inflammatory dose, and showed that in a
23 significant number of individuals treatment of pain
24 itself was sufficient, looking at pain as a major
25 component of the study.

1 This was then utilized by the American
2 College of Rheumatology criteria committee on which I
3 had the privilege of serving and which are now
4 reviewing the guidelines. And the first treatment,
5 pharmacologic treatment recommended after things like
6 weight loss, activity, exercise, and so on, is simple
7 analgesic. Not analgesic anti-inflammatory but
8 analgesic. Once again, showing the primacy of pain in
9 OA as a model of pain for study.
10 Now, given this background, let's look at
11 the data that we're presented this morning in terms of
12 study of OA as a model in this disease. A short-term
13 multiple dose study designed for this study on a daily
14 basis.
15 If we can have slide 1076, please. Is
16 anybody listening? There we go.
17 We defined the short term mobile dose
18 model of OA flare -- I think, Doctor Liang, you're
19 absolutely correct. That if you flare, you become an
20 acute pain model. I think just like description of
21 what a flare is. And in each of the osteoarthritis
22 studies, O-20 in the knee, O-21, a second knee study,
23 and O-54 in the hip, there was efficacy demonstrated
24 versus placebo as early as day one regardless of the
25 index joint.

1 Now, it was pointed out this morning that
2 if you look at worst pain, this was only significant
3 in one of these studies. However, if you look at
4 pain, average pain, over the previous 24 hours, it was
5 significant in O-21 and in O-54, in two of the studies
6 it was replicated. So, there were data there to show
7 that it was effective for average pain.
8 We also looked at worst pain and pain now.
9 These can be confounding evaluations, particularly
10 early, because you may have done something in the last
11 half hour that gives you pain or something, or you
12 have pain that started the day before. Average pain
13 in the previous 24 hours gives you the pain under the
14 curve. It's the primary question asked, for example,
15 in the WOMAC pain scale, Western Ontario McMaster Pain
16 Scale, what is your pain in the previous 24 hours.
17 Was your pain walking? Was your pain sitting? Was
18 your pain standing?
19 So, there's relevance to this looking at
20 the average pain. In that case, as I mentioned, there
21 was replication of efficacy in two of those studies
22 for analgesic effect.
23 Now, Searle was asked by FDA to look at a
24 dose response analysis to see whether you could detect
25 a difference in dose response which would support the

1 pain as a model, OA as a model, if you could show
2 this. So, the sensitivity of the model was confirmed
3 by a dose response regression analysis of covariance
4 on the pooled studies as shown the next slide. And
5 this would be slide 1068.
6 Here we see a dose response curve. Now,
7 this is day one, day two, day seven, and I'll fill in
8 days three to six on the next slide. But here we see
9 a dose response regression analysis on Celecoxib, 50
10 milligrams twice a day, 100 milligrams twice a day,
11 200 milligrams twice a day. At day one, doing this
12 regression analysis at covariance, it reached a P
13 value of 0.07, close to .07 -- .05, rather. At day
14 two it then achieved less than .01 and frequently even
15 better on P value.
16 If we can have the next slide, please.
17 Here, we see the analysis as mentioned in
18 day one, day two, three, and here was .07 and then was
19 consistently true. And, after day two, was true not
20 only for average pain in the previous 24 hours, but
21 also for worst pain and pain now. So, it became
22 concordant at day two but was positive in two cases,
23 replicated in two of the studies, 021 and 054.
24 May I have the next slide, please. This
25 would be 1077, I think.

1 Accordingly, the short term OA flare pain
2 model was able to demonstrate responses by dose and
3 the data validates the hypothesis that pain in
4 osteoarthritis respond similarly, regardless of the
5 index joint.
6 Can I go back to a slide now. I'd like
7 slide 223, and to finalize my presentation here.
8 Why should OA be a pain model? Why -- And
9 Doctor Abramson, you mentioned what about
10 inflammation. Inflammation is present in
11 osteoarthritis. I think that's why agents like non-
12 steroidal anti-inflammatory drugs, agents like the
13 COX-2 inhibitors have the potential to be better than
14 analgesics alone because they treat inflammation s
15 well.
16 On the other hand, a great deal of the
17 pain in osteoarthritis, which is multi-factorial, is
18 not -- Can I have that slide there, slide 223? No,
19 I'm sorry. That's not the model we want.
20 At any rate, let me finish up, then, by
21 saying, pain is multi-factorial. What causes pain
22 that's non-inflammatory, non-steroidal arthritis?
23 There are a number of causes. One is bone. Bone has
24 subchondral fractures, subchondral sclerosis, so you
25 get pain. Secondly, you have intramedullary

1 hypertension. An increased venous pressure in bone.
2 If you cut across the bone and do an osteotomy, you
3 get instant relief of pressure, you get instant relief
4 of pain.
5 There's periosteal stretching from
6 osteophytes. There's muscle spasm. There's soft
7 tissue deformity, particularly ligament elasticity and
8 stretch. There's also meniscal damage that occurs in
9 osteoarthritis of the knee. In addition, you have
10 distention of the capsule which is non-inflammatory.
11 So, there are many, many parameters of OA that are
12 responsible for non-inflammatory pain.
13 I might mention that in looking at pain
14 models, the fact that OA may have inflammation doesn't
15 take away from it as a model because most of your pain
16 models do have inflammation. If you have post-dental
17 extraction, for example, or post-episiotomy, or post-
18 surgical, or post-orthopedic, you have inflammation
19 plus pain.
20 So, in summary, I respectfully submit that
21 osteoarthritis has been -- this is not a new concept--
22 has been considered to be a model of pain, acute,
23 short term pain, requiring multi-dose levels of
24 administration and would be very appropriate for
25 consideration as the second model. Not only

1 appropriate, but as a model which has stable pain, is
2 almost better than post-operative or post-surgical
3 models where you have a diminishing pain over a few
4 days which confounds the ability to do the studies.
5 I'd like to ask Doctor Sunshine if he'd
6 just take a minute or two, then, to put this in
7 perspective in terms of acute pain models and short
8 term multiple-dose models in interpreting the data.
9 DOCTOR SUNSHINE: Thank you, Rollie.
10 Doctor Fernandez-Madrid said we have to
11 talk -- keep to the real world. And I think that the
12 analgesic guidelines are undergoing change. And
13 they're undergoing change because the change in the
14 rendering of medical care. The length of stay has now
15 gone down so that in New York they had to legislate
16 that women stay long enough to deliver their babies
17 before they're sent home.
18 And, in post-op pain, it's quite -- it's
19 not quite that bad. And also, the surgical techniques
20 have gotten better. I mean, the cholecystectomy was
21 a great pain model. I mean, they made a Hawkey
22 incision 12 inches long and all they had to do was
23 turn the patient and they would have pain for two or
24 three days to fulfill Doctor Delap's request.
25 Nowadays, cholecystectomies are done with a one inch

1 incision and before you go around to see them the next
2 day, they're home.
3 So, if we want to continue to evaluate
4 analgesics, I think we have to keep pace with the
5 changing delivery of health care.
6 If I may have slide 40.
7 I just want to review the dental studies
8 and I want to thank Doctor Averbuch for his review of
9 the data. But, in keeping with Doctor Delap's
10 question, we're going for a BID indication so I want
11 to enhance the data to show you 12-hour data and not
12 only the 8-hour data that was shown earlier by the
13 FDA.
14 In blue, you see the Celecoxib 200
15 milligram dose which is significantly better than
16 placebo for the full 12 hours. We agree that sodium
17 naproxen and ibuprofen in the first three or four
18 hours are a more effective analgesic. But if you look
19 at 12 hours, the mean scores for Celecoxib is greater
20 than that of ibuprofen which has a shorter half life.
21 And if you look in study 070, naproxen and Celecoxib
22 200 are similar at 12 hours. And there is a slight
23 advantage to the naproxen group here in study 027.
24 If we go on, now, to slide 1064, and this
25 is an abstract from page 23 of the guidelines. And

1 John Harter always told us it's not a cookbook but I
2 just want to take the opportunity to refresh the
3 committee's -- the requirements that one wants to meet
4 in terms of multi-dose short term therapy.
5 The guidelines suggest that the pain model
6 should be, for multi-dose short term therapy, should
7 be those which typically require several days of
8 therapy. Because continuous hourly pain measurements
9 may not be feasible with multiple dosing, a dose-to-
10 dose global evaluation of analgesia should be used.
11 The daily global assessment of analgesia could also be
12 used. And as Rollie pointed out earlier, that is
13 exactly what was done with the average pain.
14 In terms of the hourly pain and to be sure
15 that this is a drug that is suitable for BID dosing,
16 we submit the three pivotal dental studies.
17 Thank you.
18 ACTING CHAIR ABRAMSON: I just have a
19 question I guess for Doctor Needleman to field.
20 As I recall the data in the post-operative
21 pain model, there was not efficacy of Celecoxib. Can
22 you go over that again?
23 DOCTOR SUNSHINE: Yes, Doctor Abramson,
24 I'm glad you raised that question because it speaks to
25 what I talked about.

1 The sponsor wanted to complete this study
2 before the year 2000. So, they went ahead and did a
3 multi-center study. In order to get sufficient
4 patients, they enlisted 15 different centers. Some
5 centers contributed one patient. I mean, it will
6 never work and it didn't work. And if we could have
7 the slide for study 028 -- the number I don't have but
8 I know the study -- you will see that the problem was
9 the placebo response in the first four hours which is
10 as good as any. It was not significantly different
11 than any of the actives, including the combination of
12 hypoxifene and acetaminophen.
13 This is what we're talking about. If
14 you're going to insist on post-op pain and do multi-
15 center studies with 15 investigators, all the drugs
16 are going to look alike.
17 ACTING CHAIR ABRAMSON: Doctor Silverman,
18 do you have a question?
19 DOCTOR SILVERMAN: Yes. This is a
20 question for the statistically challenge, or from the
21 statistically challenged, actually.
22 For Doctor Moskowitz, you used your P
23 values on analysis of variance. Why? Why not -- I
24 mean, if you were trying to get at that there's a dose
25 response from it, I can understand. But I'd like --

1 is the analysis also an absolute the same?

2 DOCTOR MOSKOWITZ: Thank you. I'm going

3 to call on Doctor Zhao, William Zhao, who worked with

4 us on this statistical data. I'm working on this to

5 do osteoarthritis and analgesia without being a

6 statistician.

7 DOCTOR ZHAO: Thank you.

8 The dose response analysis is -- one issue

9 with any model is that model is sensitive enough to

10 pick up the difference. So, to confirm that, this

11 dose response analysis, to show you, even with the

12 difference within the active treatment groups we are

13 able to show a difference over a shorter period of

14 time. This method is actually more widely used than

15 when you don't have a placebo control, an active

16 control. In all cases, we have active control and

17 placebo controls. So you can see the difference with

18 active and placebo which confirms the validity of the

19 model.

20 So this dose response is just to further

21 confirm the validity of the model. Basically, the

22 comment is with this model, we can pick up even a

23 smaller difference between treatments groups.

24 DOCTOR MOSKOWITZ: Let me just add to that

25 a little bit. There was no study by treatment

1 difference in the groups, the hip-knee and knee
2 studies, for example. We did not use placebo in the
3 analysis. We were comparing the three doses of
4 Celecoxib, rather than to compare it to placebo, which
5 is the reason that we could go ahead and do this kind
6 of statistical analysis and regression study
7 DOCTOR SILVERMAN: I understand the
8 statistics, but we're coming back to that famous word
9 people use, relevance. If it's no better than
10 placebo, does it matter if you get a dose response
11 curve?
12 That was the heart of the question. I
13 mean, you didn't present data, as I saw it, maybe I
14 missed it. I apologize if I did -- to show that it
15 was better than placebo.
16 DOCTOR MOSKOWITZ: No, I think it -- I'm
17 sorry if that didn't come across either in the
18 excellent presentation by the FDA this morning or in
19 the presentation by the group.
20 There was a statistically significant
21 difference in pain in knee study 021 and hip study 054
22 on day one. On day two, there was a statistically
23 significance difference in worst pain, average pain in
24 the previous 24 hours, and pain now, from day two
25 through and including day seven, over placebo.

1 Statistically significant for each study, not even for
2 pooled data. So there's no question that they had an
3 analgesic effect, and it was a very consistent
4 concordant analgesic effect.
5 DOCTOR DELAP: If I might just interject
6 here.
7 I think, again, in the OA models, I think
8 we have to make sure we're differentiating between
9 acute and chronic pain. I think clearly the chronic
10 pain of OA is part of the way you assess the
11 effectiveness of your treatment. And I think we've
12 already decided we think the product works in chronic
13 use in OA.
14 For, again, the acute pain indication,
15 we're talking about well, what about if you take a
16 dose now, when are you going to experience relief and
17 how long lasting is that going to be. And when are
18 you going to have to be dosed again. Again, acute
19 analgesic features.
20 And with that in mind, again, we did try
21 and look at the three studies that looked at daily
22 pain assessments to see if those could subserve the
23 need for the acute pain models. And again, as per our
24 presentation this morning, we found that we couldn't
25 use that. Apparently one of the studies, I believe it

1 was 054, did give statistically significant results in
2 four of the five APS questions. The second study gave
3 a positive result on one of the five APS questions at
4 the end of the first day. And a third study, in these
5 OA studies, gave positive results, statistically
6 significant, zero to five APS questions.
7 So we looked at that. And in fact, we
8 have -- we had some further discussions with the
9 company as time has gone by about using OA flare as a
10 pain model for these kinds of studies. And I think we
11 agree that it can be used. So that's not at issue.
12 What's at issue is what kind of results do you need to
13 look for and what kind of results do you need to
14 obtain in order to use it successfully.
15 DOCTOR NEEDLEMAN: We have a little
16 guidelines question that we had to deal with.
17 DOCTOR ALEXANDER: I'm John Alexander from
18 Searle.
19 And the question I guess we've had and
20 we've talked on the phone the other day about it was
21 the difference between the management of pain claimed
22 and acute pain. And I think we're not really trying
23 to claim that we have sufficient data in this first
24 few hours for this acute pain claim. It's a hard
25 thing to say. But, that's the thing we're trying to

1 say. Do you have to have efficacy in the first day
2 or the first few hours? Is that the point you're
3 making for acute pain versus a claim for management of
4 pain? I guess that's the distinction we've been
5 trying to think about.
6 DOCTOR DELAP: Yes, I think that's a good
7 way to look at it. And I think, again, the
8 distinction, at least in my mind and I'll ask my
9 colleagues if they have any different perceptions, but
10 for acute pain, we're looking -- again, the patient's
11 expectation is they take a dose of the medicine and
12 they feel better fairly soon. Not, like at, the end
13 of the day but within an hour or two they feel better.
14 And then that lasts. That's the expectation.
15 DOCTOR ALEXANDER: That's what I guess we
16 don't understand from the guidelines.
17 DOCTOR DELAP: Now, for the OA, I think
18 pain relief is part and parcel of the way you look at
19 the results of your studies. So, if you have a
20 positive outcome in an OA study, I think you are
21 clearly relieving the pain of OA and that's something
22 you can say. And that's one of the things we found.
23 But again, for acute pain, I think that's
24 kind of different from this kind of chronic pain of
25 OA.

1 DOCTOR ALEXANDER: I think when we were
2 looking at the guidelines, the issue becomes the two
3 models which are clearly in the regulation. And even
4 dental pain, I think there's no question that we've
5 satisfied the requirement, at least for acute pain
6 with that model. So I think the argument has been
7 using the OA flare as the second model.
8 And, you're right, it gets confusing, and
9 we talked about this the other day, between the OA
10 indication and the pain indication, and how they
11 distinguish it.
12 So I guess you're drawing distinction with
13 that question of acute pain to differentiate those two
14 states, I guess.
15 DOCTOR DELAP: Oh, yes. Again, I think it
16 goes back to what I was saying initially. That we
17 were trying to kind of parse out, perhaps, the acute
18 and analgesic effects versus the more chronic
19 analgesic and anti-inflammatory effects that may be
20 observed. And the underlying philosophy is that the
21 doses and dose intervals, and whatnot, may be somewhat
22 different in the two different settings. We want to
23 make sure that we have enough information to be able
24 to advise people how to use the product for each
25 setting.

1 DOCTOR NEEDLEMAN: That's an interesting
2 dilemma. On the one hand we talk about we should
3 evaluate the data that's presented, your own pain
4 data. The confusing part is calling for management of
5 pain. So here we have the dental pain and fulfill the
6 criteria of beating placebo in the first hour. Then
7 we have the OA flare, and even the post-orthopedic
8 surgery, where after the placebo wash-out you could
9 see the hourly improvement. And that was two doses,
10 a multiple dose. And then you, then, could see the OA
11 flare.
12 The one other point about pain is looking
13 in the context of clinical use. There, you could look
14 at a drug like Celecoxib or COX-2 inhibitors in terms
15 of risk benefit to a patient. Because, not only do
16 you have the analgesia, in many uses where it's
17 surgical, you're not going to have a platelet effect.
18 You've gotten rid of the GI complication. Here's a
19 drug without drug interactions like with Warfarin.
20 So, in the context of a usable agent, it actually
21 spreads the opportunity.
22 That it's different from drugs that are
23 formulated for fast blood levels for a quick response.
24 That's certainly true. But these drugs are really
25 designed not just for that short time period, but for

1 the hours and the days. So that's kind of the context
2 that we brought when we presented the data.
3 ACTING CHAIR ABRAMSON: What I'd like to
4 do is have one more question of Doctor Fernandez-
5 Madrid and then Doctor Lovell. And then I'd like to
6 ask each of the panel members, we'll go around the
7 room, to comment on this particular question.
8 DOCTOR FERNANDEZ-MADRID: Yes. I don't
9 have a question. I think it is a comment that I want
10 to tell you what really bothers me on this question.
11 And, when we talk about a flare of lupus,
12 I think we know what we are talking about. When we
13 talk about a flare of rheumatoid arthritis, I think we
14 know what we are talking about. When we are talking
15 about a flare of osteoarthritis, I don't think anybody
16 knows what we are talking about. And I think Rollie
17 Moskowitz outlined very well all the reasons why a
18 patient with osteoarthritis could have acute pain.
19 In addition, the patient of osteoarthritis
20 may have inflammatory pain. They may have night pain.
21 So it is a mixed bag. So I think this is very
22 troublesome to me. And I think this is something that
23 may be relevant to this.
24 ACTING CHAIR ABRAMSON: Doctor Lovell.
25 DOCTOR LOVELL: Yes, when I reviewed the

1 information from the various models you've used,
2 there's a very large black hole for me. And that's
3 what happens if you use this product to treat pain if
4 you don't have to break or have damaged bones. For
5 example, post-surgical incisional pain, headache pain,
6 or the very common use for pain medications which is
7 kind of generalized myalgia related to viral
8 infections and that sort of thing. And it may be a
9 common situation that you're in when you do pain
10 approvals and reviews.
11 But this data is very much centered around
12 bone-related pain or osteoarthritis pain. And it
13 leaves a very large deficit and if the labeling is
14 going to be restricted to that kind of pain, it's one
15 thing. But if the label is going to be more general,
16 kind of all kinds of pain, then I think I'm left in
17 the dark as to how your drug may be effective in these
18 other non bone-type pains.
19 DR. NEEDLEMAN: It's both a regulatory and
20 a design. You did see earlier that we showed efficacy
21 versus placebo in headache which was only subset. If
22 you look in the data, in the earlier data, which we
23 could bring it up and show that, it was done with
24 comparatives with NSAIDs. But beyond that, all we
25 could present is what we tested in our -- the claim

1 that relates to just the OA flare and its use in OA
2 pain.
3 ACTING CHAIR ABRAMSON: Why don't we now
4 just go around the room and ask people to comment on
5 what they think specifically about this question 2.
6 Doctor Silverman.
7 DOCTOR SILVERMAN: I think the problem I
8 have is very similar to what people addressed. We
9 have a pain model where you do cut into bone, the
10 dental pain model, and it works. We have an OA model
11 which apparently works. And we have a post-surgical
12 model which doesn't work. So, I would think that
13 restricting to the data that demonstrates that it does
14 work when bone is effected.
15 ACTING CHAIR ABRAMSON: Doctor McCarthy.
16 DOCTOR McCARTHY: I basically feel the
17 same. And I think that to find that the drug does not
18 work in the specific setting of the orthopedic injury
19 is really an exception to the data we have rather than
20 the trend. And it may be that any analgesic will not
21 work in a particular clinical situation because we
22 don't know enough about the mechanism of pain in that
23 situation. So I have no objection to the approval.
24 ACTING CHAIR ABRAMSON: So you would
25 approve it for pain.

1 DOCTOR McCARTHY: For acute pain as well
2 as OA. And I also think, returning to the real world
3 which somebody else keeps bringing up, that once this
4 things goes on a formulary as the NSAIDs on the
5 hospital formulary, it's going to be used for pain
6 whether we approve it or not.
7 ACTING CHAIR ABRAMSON: Right. We're
8 going to ask for comments and then let the sponsor
9 respond. And then we'll take a vote after everybody
10 makes their comments. So these are not final votes.
11 Doctor McConnell.
12 DOCTOR McCONNELL: I would agree and I'd
13 echo the final comment that it's possible with any
14 analgesia that one or another model may not be valid.
15 MS. MALONE: I have to say, I'm really
16 confused as to what we're discussing. Are we -- Are
17 they trying to say that they want to use it for any
18 type of pain?
19 ACTING CHAIR ABRAMSON: As I understand
20 it, it's a request for an indication for analgesia
21 with a rather broad array --
22 MS. MALONE: In general.
23 ACTING CHAIR ABRAMSON: -- of pain
24 indications.
25 MS. MALONE: Very broad.

1 ACTING CHAIR ABRAMSON: Is that correct?
2 Management of pain.
3 DOCTOR NEEDLEMAN: We're required to ask
4 for management of pain as opposed to acute pain or
5 dental pain, or OA pain and flare.
6 ACTING CHAIR ABRAMSON: So, it would
7 headache, dysmenorrhea, things like that? No?
8 DOCTOR NEEDLEMAN: No.
9 MS. MALONE: No.
10 DOCTOR SILVERMAN: That's what we need
11 some clarification on.
12 MS. MALONE: That's what we don't know.
13 DOCTOR DELAP: It's covered under the
14 indication. I mean, if it's an acute pain indication,
15 then it is viewed as covering. That's why we're
16 looking for the two different models, because we are
17 trying to get enough coverage so we feel comfortable
18 extrapolating to the full realm of acute pain. There
19 are some very specific kinds of pains we might not
20 include in there, like neuropathic pain, which is a
21 separate issue. But in general, once you've got an
22 acute pain indication, we view that as covering the
23 whole spectrum of the usual kinds of acute pain.
24 DOCTOR NEEDLEMAN: The question is, can
25 you look at management of pain but with the specifics

1 of covering dental pain and the pain of OA in flare
2 so you really put precision around it based on the
3 actual data.
4 DOCTOR DELAP: All I can answer is what I
5 think has been the precedent so far, and certainly
6 things can always change. But the precedent has been
7 that the pain in the setting of OA is, again, part and
8 parcel of the OA signs and symptoms indications. So
9 if you have that indication as the committee has said
10 we should have, then you are covered in terms of pain
11 of OA.
12 The acute pain is kind of a large category
13 of a variety of things that cause the person to get
14 acute pain. Dental pain is one and post-op pain is
15 another. Dysmenorrhea is another. And again, there
16 we, at least historically, have looked for persuasive
17 results in two models after which we give you the
18 whole category of acute pain.
19 And I guess at this point in time we're
20 saying that OA flare, if studied appropriately and the
21 results are supportive, could also be one of the two
22 models. So that's, again, that's not an issue for us.
23 What's at issue is the results of the OA flare and
24 whether we do in fact have two models here.
25 I guess to put our cards on the table, we

1 think that the results are supportive of an acute pain
2 model but by precedent, our expectation would be
3 probably require one additional study at this point
4 saying what is available. So far it is part of the
5 way there but not entirely there, and perhaps one
6 additional study, say in OA flare, performed as an
7 acute pain kind of study might be all that would be
8 needed to finish that up.
9 ACTING CHAIR ABRAMSON: Doctor McCarthy.
10 DOCTOR McCARTHY: I think in this
11 discussion, three people have now mentioned
12 dysmenorrhea. And I must say, this is a rapidly
13 changing game. And I don't think we should lump this
14 with the other pain indications because the big
15 question here right now is do NSAIDs cause anovulatory
16 cycles? I mean, much of the dysmenorrhea has been
17 linked to both mittelschmerz and premenstrual pains.
18 And certainly the large animal veterinary world is
19 already looking into the use of selected COX-2
20 inhibitors to control the time of ovulation.
21 So, I think we have to be very careful
22 right now about dysmenorrhea until we know a bit more
23 about what selected COX-2 inhibitors are doing to
24 women who are still childbearing.
25 ACTING CHAIR ABRAMSON: So just in terms

1 of trying to get some clarity here. From the FDA's
2 vantage point, what's being requested is a management
3 of pain indication which is rather overarching, which
4 would include dysmenorrhea, headache?
5 DOCTOR HYDE: No, it would not
6 necessarily.
7 ACTING CHAIR ABRAMSON: I'm sorry.
8 DOCTOR HYDE: Dysmenorrhea would need to
9 be studied separately but could count as a model.
10 ACTING CHAIR ABRAMSON: Oh, I
11 misunderstood, then, what you said. I thought you had
12 said that the pain indication was a rather broad one
13 ultimately.
14 DOCTOR HYDE: Yes, it is. Although if
15 dysmenorrhea is studied, it's mentioned explicitly as
16 an indication.
17 DOCTOR LOVELL: But if it's not studied,
18 then the indication will read: "For the treatment of
19 acute pain" and dysmenorrhea is certainly an acute
20 pain situation in which this drug will be used,
21 correct? Or could possibly be used?
22 DOCTOR HYDE: That's right. In many
23 things -- I mean, that's the problem with how we do
24 it. Pain is a symptom. If you study something with
25 more or less a diagnosis then that would deserve

1 explicit mention. It's a problem in how do you
2 generalize, really, from just studying one
3 particular --
4 DOCTOR DELAP: Again, the indication in
5 our traditional view, at least, has been acute pain.
6 And certainly you can present the data that you have.
7 And if you never studied dysmenorrhea, then you can't
8 present data saying that you've shown that it works in
9 dysmenorrhea. But, again, the indication is acute
10 pain and we view that as covering the variety of acute
11 pains that we all get from day to day as opposed to
12 parsing out all of the separate possibilities. If
13 science shows that dysmenorrhea should be considered
14 differently and is no longer the kind of thing you
15 should consider as an appropriate model, then you have
16 to look at that. But I'm not prepared to talk about
17 that right now.
18 DOCTOR TILLEY: I guess I'm hearing sort
19 of a catch-22 for the company here because I don't
20 hear them wanting to generalize to the entire world of
21 pain and yet I see them sort of being forced to by
22 choosing between either management of pain or nothing.
23 It seems to me that I would be more comfortable being
24 driven by the data in choosing an intermediate step
25 which would be pain of -- chronic pain of

1 osteoarthritis and dental pain. And not having to go
2 to this broad general term that could be interpreted
3 by the outside world as anything.
4 ACTING CHAIR ABRAMSON: But that's the
5 question being placed before us right now.
6 DOCTOR TILLEY: I guess as a committee we
7 can devise whatever we want. They don't have to
8 listen to us.
9 ACTING CHAIR ABRAMSON: Excuse me one
10 second. Ms. Malone has been waiting.
11 MS. MALONE: It's just the problem, again,
12 people getting sort of a blanket statement saying that
13 no matter what kind of pain I have, oh, I can take
14 this. And is that what we mean to do? Because that
15 hasn't been shown that it can cover any type of pain.
16 DOCTOR DELAP: Well, unfortunately
17 regulation is not an exact science and I think it
18 would be unfair of us to ask companies to study ever
19 conceivable model in order to get a pain indication.
20 So, this is, to some degree, I guess, a compromise
21 saying that if you study two models that we agree are
22 good models and are well studied, one of which is the
23 kind of pain that comes and goes fairly quickly so you
24 might just need one or two doses, and another one is
25 pain that might last for some period of days where you

1 need repeated dosing, then we have the information we
2 need to say it's been studied in pain and this is the
3 way you dose it to get the analgesic effect.
4 So it is a compromise and I think we
5 recognize it as such. In a perfect world, I guess
6 you'd study in every different conceivable situation
7 and have all the data for all patients. But this is
8 admittedly a kind of a compromise.
9 DOCTOR SPIVEY: Can I offer something?
10 Rich Spivey from Searle.
11 The '92 analgesic guideline really speak
12 to labeling. And historically, our understanding of
13 these guidelines is that the pain indication is for
14 the management of pain and you describe the types of
15 pain models that were used in the labeling.
16 Now, we've been talking about acute pain
17 and so, and we didn't -- we never have viewed it that
18 way. We really have followed these guidelines in
19 terms of the labeling request. So, the other thing
20 that we have a complete understanding from our
21 perspective is that dysmenorrhea is in fact a
22 different indication. And in the market place, you
23 cannot go out and target that population unless you
24 have that specific indication.
25 That's just our perspective on it and the

1 management of pain, I understand it's a difficult
2 discussion here, but it's really based upon the
3 guidelines and the way labeling is presented in that
4 particular guideline and how that information is going
5 to then be communicated in the label.
6 ACTING CHAIR ABRAMSON: Doctor Liang. No?
7 Okay.
8 Doctor Harris.
9 DOCTOR HARRIS: Well, my view is
10 unquestionably the data does support the -- having an
11 analgesic effect. But I'd like to make a comment,
12 too. I was rather disappointed when one compared it
13 to Naprosyn or even Motrin at 400 milligrams a day,
14 or, 400 milligrams in a .4h, that in fact it wasn't as
15 effective. And one wonders why not Tylenol which, of
16 course, is safe and analgesic. And this is merely a
17 reflection indeed. I mean, in terms of analgesia, I
18 would say that it certainly does appear appropriate
19 for pain use. I was disappointed in its relative lack
20 of effectiveness.
21 ACTING CHAIR ABRAMSON: Doctor Fernandez-
22 Madrid, do you have any further comment?
23 DOCTOR FERNANDEZ-MADRID: No, I have no
24 further comment.
25 DOCTOR LOVELL: Well, I have, I think,

1 perhaps there's a middle ground here between the
2 catch-22 that somebody mentioned and a very specific
3 label that says only dental pain and osteoarthritis
4 flare pain. And that is perhaps to request another
5 study be done that has nothing to do with broken
6 bones. Because a large amount of the use of this
7 drug, I think, if it is approved for acute pain, will
8 be in non-orthopedic, non-bone indications. And the
9 reviewers are kind of left in the dark, and the
10 consumers I think will be left in the dark, as to
11 whether it may be efficacious in that group or not.
12 I have a question. And that is a common
13 concurrent medication in this pain indication would be
14 acetaminophen. And I'm wondering if you have any
15 information about drug interactions with
16 acetaminophen?
17 DOCTOR KARIM: We do not have an
18 interaction study with Celecoxib and acetaminophen
19 because acetaminophen is not metabolized by a 2C9.
20 But there has been a recent report in the New England
21 Journal of Medicine that there is a marked significant
22 interaction between acetaminophen and Warfarin.
23 ACTING CHAIR ABRAMSON: So no known
24 interaction between COX-2 inhibitors with Celecoxib?
25 DOCTOR KARIM: No, we don't have any

1 information on Celecoxib and acetaminophen, and it is
2 not expected to have an interaction. Based on the
3 isoenzyme involved in metabolizism of acetaminophen.
4 DOCTOR LOVELL: I have another comment and
5 concern. And that is, there's a very significant
6 special population here that uses analgesic
7 medications quite frequently and that's the pediatric
8 population. And there's no information in the label
9 or in any of the information we've been presented
10 about what may happen if this product is introduced in
11 children. And my concern is if it gets an acute pain
12 indication, that in all likelihood it will be given to
13 a large number of children.
14 DOCTOR NEEDLEMAN: Do you want us to
15 address that pediatric question now?
16 ACTING CHAIR ABRAMSON: I think we should
17 wait on that.
18 DOCTOR LOVELL: We need to address the
19 pediatric question at some point. If we would defer
20 that question, fine with me but I think we need to
21 address it at some point. And I don't -- it can be
22 later.
23 ACTING CHAIR ABRAMSON: Phil, do you want
24 to make a comment?
25 DOCTOR NEEDLEMAN: Very quickly. We

1 really have no trials now. That would be planned
2 after the submission to do a pediatric and to do
3 juvenile arthritis.
4 ACTING CHAIR ABRAMSON: Doctor Liang had
5 to leave but he did leave his brief comment. He did
6 not agree that additional studies were necessary. He
7 thought the osteoarthritis model was sufficient.
8 I'm very confused. I think there's a lot
9 of issues, to me, that are still between the sponsor
10 and the FDA on this. I'm not yet convinced that the
11 OA model is so clear because of the multi-factorial
12 nature of the pain. So I would -- my own view would
13 be to defer this kind of question to further
14 discussions. I would tend, therefore, to agree that
15 more data, at least more discussion, would be
16 necessary.
17 DOCTOR PUCINO: I agree. I think more
18 data also is necessary.
19 ACTING CHAIR ABRAMSON: Any comments?
20 DOCTOR NEEDLEMAN: Steve, anybody have a
21 last comment?
22 DOCTOR McCARTHY: Just to put this in some
23 perspective, if you look at the market research data
24 from people like Walsh America or INS, about 75
25 percent of all NSAIDs are used for less than 30 days

1 and the majority, almost 75 percent, is used for pain.
2 And it's mostly for acute musculoskeletal strain. So,
3 in fact, although there are a large number of other
4 indications, the big one is acute musculoskeletal
5 pain, injury, that sort of thing. And if another
6 trial were to be done, I would favor doing it in that
7 group of patients.
8 ACTING CHAIR ABRAMSON: And I would just
9 elaborate on that. My concern is that we do have an
10 approval. We've tentatively, or we've made the
11 recommendation to approve for osteoarthritis and that
12 this drug would be used for many different kinds of
13 pain and right now we have only the dental model
14 that's clearly a traditional model. So that's my only
15 hesitancy.
16 Doctor Sunshine.
17 DOCTOR SUNSHINE: I would like to say the
18 following. The sponsor, based on the guidelines,
19 should provide, and I'm reading from the guidelines,
20 substantial evidence for the efficacy of a new
21 analgesic. Several different pain models should be
22 represented among the successfully controlled trials
23 on the analgesic efficacy. It is desirable to explore
24 the use of the test drug in as many models as
25 possible.

1 I would like to argue that we're ahead
2 that we didn't study dysmenorrhea as a pain model.
3 There is the argument that you made, but more
4 importantly, dysmenorrhea occurs in women, not in men.
5 It occurs in women of childbearing potential. You're
6 really not getting the spectrum of how this is going
7 to work in the general population. The OA model takes
8 patients from 65. I think the mean age was 65. It's
9 a much different age population.
10 More importantly, and I think Doctor Delap
11 asked the sponsors to see if we could achieve a dose
12 response. And the regression analysis was
13 significant. So there was a dose response of 50 to
14 100 to 200 showing assay sensitivity.
15 Doctor Melich here who's done a great many
16 dysmenorrhea studies rarely is able to pick up a dose
17 response with ibuprofen in dysmenorrhea. You have to
18 start with a higher dose and you do not get a dose
19 response. So we have a better model than
20 dysmenorrhea. We have men and women of a wide age
21 range and we have dose response. And I don't know
22 about your dentist, but when my dentist took my teeth
23 out, he didn't break my jaw.
24 So, I don't think the dental model
25 represents broken bones and I think Doctor Dione is

1 here from the NIH, and he can tell you about his
2 studies of inflammation in the extraction model. And
3 that's what we're talking about. We're not talking
4 about a broken jaw. We're talking about inflammation.
5 So you have two models, quite varied,
6 different age group, different sex. I think you
7 fulfilled the requirements of the guidelines and I
8 think -- and the other point is, the headache studies,
9 if you want a headache claim and I don't think the
10 sponsor is entitled to it, you need headache studies.
11 If you want a dysmenorrhea claim, you need
12 dysmenorrhea studies. But if you want a general
13 claim, you see, you have the evidence.
14 ACTING CHAIR ABRAMSON: I think, just to
15 bring this to some closure, the difficulty that I as
16 a panel member and perhaps others have, is that the
17 FDA has a traditional way of doing business in this
18 area of approval and we are debating here whether a
19 new model being presented which we've already approved
20 for one indication can also be used as a pain model.
21 And maybe it can, maybe it can't. But I think that
22 needs to get debated and discussed, and maybe more
23 data is needed, maybe not. But I think that becomes
24 something that the panel really can't address in a
25 meaningful way other than just to give these kinds of

1 opinions.

2 So, I think you've heard some of the

3 opinions. If you'd like a vote, we can do a vote.

4 But my sense is that this is --

5 DOCTOR NEEDLEMAN: Can we give one last

6 statement?

7 ACTING CHAIR ABRAMSON: Of course.

8 DOCTOR NEEDLEMAN: From Steve Geis.

9 DOCTOR GEIS: I'd just like to comment

10 just on the whole concept of a model being a valid

11 model.

12 And, having done some of these post-op

13 studies as well as the dental pain model in the OA,

14 the OA model has consistently been right on target and

15 reproducible. That is something you usually don't see

16 and the literature tells us about some of these other

17 post-surgical models. We see in the literature that

18 sometimes you have to do five and six studies with

19 compounds we really do know work in an acute setting

20 in order to see them work again in some post-op study.

21 So, those models, I think, are even

22 questionable of what they really mean if they can't be

23 reproducible. And in our experience, the dental pain

24 really was and certainly the OA acute flare model was

25 reproducible and right on target every time.

1 ACTING CHAIR ABRAMSON: I ask what you
2 would like to hear from the panel at this point?
3 DOCTOR DELAP: I think it's -- we offer
4 the questions simply to see what advice we can get.
5 And you're not required to take a vote on it if you
6 don't wish to. In any event, we'll be working with
7 the sponsor to see if we can't come to a meeting of
8 the minds on this issue.
9 ACTING CHAIR ABRAMSON: My own impression
10 is that discussion should go on between the FDA and
11 the sponsor. But I'm opened to anybody on panel that
12 feels differently and thinks that we should take a
13 vote on it.
14 If that was difficult. Number three. At
15 the prior AAC meetings on the subject, endoscopic
16 studies have been viewed as surrogates of clinically
17 meaningful endpoints. Given that Celecoxib, in these
18 endoscopic studies, has demonstrated consistent
19 statistical superiority to only two of the three
20 NSAIDs studies, what comparisons, if any, should be
21 allowed in the labeling between Celecoxib and these
22 NSAIDs? Can these data be extrapolated to make
23 comparisons between Celecoxib and all other NSAIDs?
24 So, who would like to begin with
25 questions?

1 Doctor Silverman.

2 DOCTOR SILVERMAN: Are all -- I guess my
3 question is to the sponsor. Are all NSAIDs
4 comparable? And my knowledge is that they're not.
5 Therefore, how could one, then, ask the question to
6 compare to all NSAIDs?

7 DOCTOR NEEDLEMAN: Good question. I think
8 actually you're going in order of intensity of the
9 questions so endoscopy seems the right place to be.

10 Actually, Steve, first we'll hear from
11 Steve Geis and then we'd like to hear from some of our
12 consultants about the endoscopy.

13 Steve.

14 ACTING CHAIR ABRAMSON: And repeating the
15 question, are all NSAIDs comparable and really taking
16 a look at all the implications around endoscopy.

17 DOCTOR GEIS: So, I can just talk about
18 the experience that we've had as we've studied
19 cytotech and arthrotech over the years. And I think
20 one of the studies that really comes to mind for me is
21 a big study we did in the late 1980s where we took
22 1,800 patients who were taking NSAIDs and we simply
23 endoscoped them, and look at the point prevalence of
24 ulceration at that time. And we were sort of
25 expecting to see differences between NSAIDs because

1 had heard, like everybody else, that some are safer
2 than others. And lo and behold, that really was not
3 the case in that setting.
4 And if I could see the slide, I think we
5 have the results of that particular analysis. And
6 what this shows is the point prevalence of ulcers with
7 various NSAIDs that patients had been taking. And
8 yes, this was a prospective study and it wasn't
9 balanced in terms of the types of NSAIDs. But
10 nevertheless, there was a significant number of
11 patients who were taking these various NSAIDs and they
12 all came in at about 20 percent.
13 Slide off, please.
14 And that's consistently what we have been
15 seeing over the years as we repeatedly do these
16 endoscopy trials. We see about 20 percent incidence
17 of ulcers in a point prevalence type of experience.
18 And we're also finding that even NSAIDs
19 that we think are really safe, and we've recently
20 completed a clinical trial against Nabumetone and we
21 have also shown that the incidence of ulcers for that
22 compound is also much higher than people had
23 experienced or expected before.
24 So I guess I'm becoming more and more
25 convinced that they really all do look alike. And

1 again, I think, and at one point we've been in
2 discussions with various health agencies and they have
3 stepped forward and said that they think certain
4 NSAIDs are safer than others. And, for example,
5 ibuprofen we used in our studies at the request of
6 FDA. And as you saw, the ibuprofen data from our
7 serial endoscopy trial, for sure, certainly had a very
8 high incidence of ulcers.
9 So, Doctor Silverstein, I think, would
10 like to comment on this as well.
11 DOCTOR SILVERSTEIN: We've really raised
12 about 15 questions at one time. But I'll try to focus
13 on this one issue which has to do with how many NSAIDs
14 do you have to study to feel like you've studied a
15 whole group of NSAIDs.
16 And, I would echo what Steve Geis just
17 said. My experience as a watcher of complications in
18 GI bleeding over the last 25 or 30 years has been that
19 when a new NSAID is brought out, it typically is
20 reported as being safer than other NSAIDs. But,
21 unfortunately, at least my reading of the literature
22 has been, it's been used at lower doses, often at
23 analgesic doses. And when the dose is increased to
24 anti-inflammatory doses, that the incidence of
25 ulceration and of ulcer complication tends to

1 increase. And so, the initial enthusiasm cannot be
2 supported.
3 And I think that my impression as a
4 gastroenterologist with an interest in GI bleeding is
5 that there in fact is not a gold standard, very safe
6 NSAID. A recent paper by Croyer and Feldman in the
7 American Journal of Physiology -- American Journal of
8 Medicine, rather, did some elegant studies of COX-1
9 and COX-2. And it kind of agreed that at least at the
10 time of their study, none of the NSAIDs had emerged as
11 being especially safe.
12 Now, in fact, ibuprofen is probably the
13 NSAID that is most widely -- one of the NSAIDs that's
14 most widely quoted. And if you could put up slide
15 142, please.
16 I think you can see a couple of the
17 studies, there have been four or five papers by
18 Langman and a variety of other authors including Fries
19 and Henry which have suggested that ibuprofen looks to
20 be a bit less injurious than, by toxicity index and
21 relative GI toxicity, than other NSAIDs. And yet,
22 when the dose of ibuprofen is increased, we tend to
23 see ulcerates, like Steve Geis just showed us, which
24 is still 20 percent.
25 So, there is a sort of a paradox here of

1 this kind of study or the study by Langman which
2 suggested that ibuprofen is the safest of the NSAIDs.
3 And yet, when studies are done prospectively looking
4 at ulceration rates, they're similar to other NSAIDs.
5 So, I think then, in conclusion, that
6 studying ibuprofen which is said to be one of the
7 safer drugs, naproxen which is one of the most widely
8 used NSAIDs in the United States, and dyclofenac which
9 is one of the most widely used NSAIDs in the rest of
10 the world, that that's a pretty reasonable group. And
11 I think Larry Goldkind suggested that, in his opinion,
12 that was a reasonable selection of NSAIDs as well.
13 ACTING CHAIR ABRAMSON: Doctor McCarthy.
14 DOCTOR McCARTHY: I'm going to deal with
15 the first part of the question, just the first two
16 lines.
17 I have for ten years been an outlier on
18 this question so I freely admit my bias. I do not
19 think the lesions seen that are erosive are a
20 predictor of clinical outcomes. I have never believed
21 in surrogate markers. And I will try in a brief time
22 to justify that position.
23 I, unfortunately, didn't know this game
24 very well before coming here, so I haven't brought any
25 slides. But I will try to marshal some arguments.

1 Now, the first problem is that if we go to
2 endoscopic studies, the prospect of incident studies
3 or prevalent studies of lesions at endoscopy are very
4 high. They show, if we include minor hemorrhagic
5 lesions, erosions, gastric ulcers, duodenal ulcers, et
6 cetera, up to 60 percent of patients on NSAIDs had
7 endoscopic lesions. And I would accept Doctor
8 Silverstein's study, the statement that perhaps 20
9 percent of these are gastric erosions.
10 But the point is, that despite this
11 extremely high rate in prevalent studies, the number
12 of serious adverse outcomes is very low. It's
13 arguably somewhere between 2 and 6 percent per annum
14 if we were to take the FDA's database which was
15 provided here by James O'Neil in 1988, which showed
16 prospective IND studies of eight different NSAIDs in
17 the U.S. and the confidence intervals for significant
18 hospitalizing effects at one year were between 2 and
19 6 percent.
20 So let's take the 2 percent figure, even
21 the lowest. Two percent is a lot less than 60
22 percent. And we also know that the crude risk data by
23 Langman and others suggest that the risk of a
24 significant adverse event after one bad -- even after
25 one ingestion is about one in 5,000 NSAID users. So,

1 the risk of a really bad outcome is very low in
2 contrast to the high prevalence. Now, why is this?
3 Well, one of the other things that
4 gastroenterologists don't like is the word NSAID
5 gastropathy. We think this is a smear term that
6 buries a number of quite distinct clinical problems.
7 The first problem is the anti platelet effects of
8 these drugs which cause bleeding. And they do so even
9 in low-dose aspirin studies, like the U.K. TIA study,
10 down to 30 milligrams per day shows some bleeding.
11 And, of course, it's a dose responsive effect.
12 But the point is that the doses associated
13 with an increase in bleeding are far less than the
14 doses associated with a clinically significant ulcer
15 which comes to surgery.
16 Now, we also have the problem of NSAID
17 ulcers, meaning that there are lesions caused by
18 NSAIDs. I do not believe that the NSAIDs are all the
19 same in this regard. I think some, like pro drugs
20 like clinoril, relafen, and todelac, et cetera, have
21 actually very much lower rates of acute erosion injury
22 in Lancet type studies. And yet, even though these
23 drugs are endoscopically fairly benign in the first
24 instance by three months, many of them do have
25 significant outcome, adverse outcomes, associated with

1 them.

2 And usually it's not diffused lesions that
3 cause the trouble. It's solitary, large ulcers in the
4 anterium or in the pyloric channel. And I think the
5 natural history of these conditions is different from
6 that of acute erosions. It was, in fact, noted
7 recently in the Hawkey study in the New England
8 Journal that misoprostol was in fact more efficacious
9 against erosions whereas the proton pump inhibitors
10 were more effective against clear gastric or duodenal
11 peptic ulcers.

12 So, the third thing that comes into this
13 issue is that there are peptic ulcers in the
14 population, and they increase greatly with age. And
15 the complication rates of serious adverse outcomes
16 increase greatly with age, even in the non-NSAID
17 population. There's a lot of confusion as to whether
18 the increase in the elderly is due to an increase in
19 the background risk and severity of peptic ulcer
20 disease with a relatively constant relative risk for
21 NSAIDs, or whether, in fact, there is an increasing
22 relative risk for NSAIDs.

23 But, I think it's very clear that there's
24 a major increase in the background risk of peptic
25 ulcer disease in the elderly even when no NSAIDs are

1 in use. And therefore, large numbers of patients who
2 are requiring these drugs have peptic ulcer disease
3 which is not easily diagnosed. We know from the ACE-2
4 antagonist studies that about half at least of the
5 peptic ulcers in the population are relatively
6 asymptomatic. And that figure may be higher in the
7 elderly.
8 So, when we talk about complications in
9 NSAIDs, we often don't now whether we're talking about
10 a bleed that was caused by a platelet problem, an
11 ulcer that was caused by an NSAID which then bled, or
12 a peptic ulcer exacerbated by NSAID therapy. And the
13 exacerbations we need to think about are, first of
14 all, the adverse effects of NSAIDs on healing. And
15 the second issue that's quite confused, and I won't
16 solve it today, but it's the whole issue of
17 helicobacter therapy.
18 Now, helicobacter comes across this in two
19 different ways in the sense that helicobacter
20 gastritis is common but seropositivity for
21 helicobacter is predictive of nothing in the absence
22 or presence of NSAIDs. So, it isn't surprising that
23 the test using helicobacter status as a predictor of
24 adverse outcome don't show very much because the test
25 has a very low predicted value anyway.

1 So, we seem to have two problems that are
2 distinct coming across the NSAID area. One is that
3 helicobacter gastritis is common but most of those
4 patients will never get an ulcer. And only about one
5 in six HP positive patients will get an ulcer.
6 But it is that group who get the ulcer
7 that are really the group we worry about. Now, five
8 out of six patients with helicobacter don't get ulcers
9 and there is even data now suggesting that the
10 helicobacter gastritis in those patients may be
11 somewhat protective against peptic ulcer. And it has
12 been shown that in helicobacter patients, COX-2 is up-
13 regulated. The prostaglandin then released into the
14 mucosa is increased. And it is also shown that
15 adverse outcomes are less in HP-positive patients in
16 drug trials than in HP-negative drug trials. There
17 are about three trials by Hawkey that show that trend
18 in the data.
19 And Hawkey has pointed out the possibility
20 that highly selective COX-2 inhibitors by getting at
21 the inflammation that was resulting in prostaglandin
22 production might in fact diminish protection to some
23 extent in these patients.
24 Now, this is definitely a confused issue.
25 But when people have looked at a lot of the risk

1 factors that have been in these studies, things like
2 helicobacter and aspirin, and so on, have been
3 examined as single risk factors in more or less
4 univariate models. But many of these are interactive
5 risk factors. There are strong interactions between
6 helicobacter and smoking. Hawkey has recently shown
7 that the relative risk of combining aspirin therapy
8 with helicobacter positivity increases the risk of
9 bleeding with a relative risk of 23.5.
10 So even lowish doses of aspirin are much
11 more dangerous in helicobacter-positive patients than
12 they are in helicobacter negative patients.
13 There are other interactions between
14 smoking and NSAIDs in perforation, and so on. So this
15 is not a simple field. But my belief is that much of
16 the bleeding that we see is due to platelet problems.
17 And I think Celecoxib will make a significant
18 contribution in that area provided it is not co-used
19 with low dose or any other kind of aspirin which will
20 immediately introduce a COX-1 inhibitor back into the
21 system and actually adversely effect the benefits of
22 having Celecoxib available. So I would certainly
23 advocate strongly against combining low dose aspirin
24 with Celecoxib.
25 I also believe that Celecoxib will produce

1 these endoscopic lesions that are seen, but I think it
2 remains to be seen whether or not they will change
3 perforations from serious hemorrhage and serious
4 perforations from pre-existing peptic ulcer disease
5 that is adversely effected by the use of NSAIDs,
6 whether selective or otherwise.
7 In the MUCOSA trial, it was interesting
8 that a great number of efforts were made to exclude
9 from the trial people with a previous history of
10 peptic ulcer disease. Despite that, the greatest
11 benefits in the trial were seen in those patients who
12 had a previous history of peptic ulcer disease. And
13 the biggest significant benefit was perforation
14 protection. And even though the numbers are small,
15 there was a clear-cut advantage in preventing
16 perforation in people with a previous history of
17 peptic ulcer.
18 So, I think underlying peptic ulcer
19 disease is a significant problem and it isn't clear
20 what will happen to the underlying peptic ulcer
21 disease in the face of selected COX-2 inhibitors. And
22 there are several experimental papers already showing
23 delay in ulcer healing caused by these agents.
24 Now, there are some other small points but
25 they need to be mentioned.

1 ACTING CHAIR ABRAMSON: Excuse me, Doctor
2 McCarthy, can I just interrupt you for one second.
3 If we -- I don't mean to not have you make
4 those points. But, can we -- do they pertain to
5 question 3? Because we -- this will come up in
6 further discussion, other issues related to --
7 DOCTOR McCARTHY: Number 3. I guess the
8 question is --
9 ACTING CHAIR ABRAMSON: It's endoscopic
10 studies of surrogates --
11 DOCTOR McCARTHY: -- are they meaningful
12 endpoints?
13 ACTING CHAIR ABRAMSON: I'm sorry?
14 DOCTOR McCARTHY: My answer is they're not
15 clinically meaningful endpoints. The clinically
16 meaningful endpoints are admissions to hospitals for
17 hemorrhage, perforation, ulcer obstruction, and, of
18 course, death is also a very meaningful endpoint.
19 That is not so easy to capture in the
20 studies from Armstrong and Blower in England suggested
21 that up to 33 percent of those dying from NSAID
22 induced catastrophes died either at home or on the way
23 to hospital or in emergency rooms. So, we don't have
24 very good data on mortality or its attributability
25 with these drugs.

1 Now, the one last point I do want to make,
2 though, is that many studies show that unlike the
3 acute lesions which are present in the stomach for the
4 most part, the majority of serious adverse outcome are
5 duodenal ulcers. Over half of them. And we don't
6 believe that NSAIDs or aspirin have much to do with
7 the causation of duodenal ulcer and yet the duodenal
8 ulcer is commonly present among those hospitalized.
9 And I would also point out that there was
10 some confusion created by the data talked about by
11 Doctor Silverstein. The study of Doctor Geis in 1991
12 showed, in fact, that a lot of these drugs had a high
13 prevalence of erosions on endoscopy. And yet, there
14 are now eight studies, including the Langman study
15 which is coded here, and the metanalysis by Henry that
16 showed that there are very significant differences in
17 the relative risks associated with these therapies.
18 So that even though the initial endoscopy
19 showed an equivalence of damage from these, the long
20 term follow up of outcomes from the therapy showed
21 distinct differences between 1 to 2 for ibuprofen, 2
22 as high as 23 for azypropizone, and recently 24.7 for
23 Teridol.
24 And Teridol is interesting because in
25 terms of selective --

1 DOCTOR SILVERMAN: Excuse me, Doctor
2 McCarthy, these are important issues because it does
3 address the variability among the NSAIDs. But maybe
4 if I could ask if we can ask the sponsor to respond to
5 some of the comments that you've made. And then
6 we'll--
7 DOCTOR NEEDLEMAN: We, of course, there
8 are a number of subsets and I think we should unpeel
9 the onion.
10 Steve, would you like to start and then
11 we'll talk about the endoscopy.
12 DOCTOR GEIS: I think the -- I mean, by
13 all means we would agree that this whole issue is
14 complicated and it's subject to a lot of debate. And
15 I think that's why we did so many studies with so many
16 people and collected so much stuff.
17 What I'd like to focus on, though, is the
18 fact that we have collected information on GI
19 complications, the ulcer complications, and the
20 experience in our hands really does match what other
21 people have seen. And if we look at the literature,
22 in the incidence of GI complications in non-NSAID
23 users -- I think I have a slide on this -- we see that
24 it comes in at a rate of about .2 percent.
25 And as we see here, this is the data from

1 the ARAMIS database and from Gutthan, is that really
2 in non-NSAID users, complications are about the .2 to
3 the .3 percent. And of interest, that's really what
4 we saw in our data, in our data in terms of Celecoxib
5 exposure.
6 Now, if you look at the literature in
7 terms of the incidence of complications with NSAIDs,
8 if I could have the next slide, you see that the
9 literature pretty much supports that that incidence,
10 as shown by the FDA, from our experience with the
11 MUCOSA trial, and the ARAMIS database, that NSAIDs
12 upper GI ulcer complications is in the range of about
13 2 percent.
14 Now, that was our experience as well. And
15 if you show the next slide, which is the results of
16 our ulcer complication analysis -- can I have the next
17 slide, please -- what we showed was that Celecoxib
18 came in at about the .2 percent, which is what the
19 literature tells us the patients not on NSAIDs come in
20 with. And I believe there's the other slide which is
21 -- that shows the incidence of complications on NSAIDs
22 in our hands comes in at about 2 percent.
23 So, I guess what I'm saying is, the
24 complications are important. We've collected the data
25 on complications. And the data that we have collected

1 on complications with NSAIDs matches other people's
2 experience. And the data we've collected on
3 complications with Celecoxib matches other people's
4 experience in terms of the background rate in the
5 general population.
6 ACTING CHAIR ABRAMSON: No, no, let's move
7 things around. But I do want to ask -- can I ask
8 Doctor Geis a question?
9 DOCTOR NEEDLEMAN: Please.
10 ACTING CHAIR ABRAMSON: I mean, while
11 you're on this information, these data, serious GI
12 bleeds or complications that Doctor McCarthy was
13 talking about, I don't recall from this morning. I
14 know it's in the papers. How -- what was the incidence
15 of these PUBs in the Celecoxib group versus your --
16 any of your active comparator group?
17 DOCTOR GEIS: So, you're specifically just
18 referring to just the GI complication?
19 ACTING CHAIR ABRAMSON: Precisely. I
20 mean, the issue is is endoscopy a surrogate? People
21 have argued in clinical studies to look at least the
22 serious adverse events. I don't recall seeing them
23 numbered clearly in my mind what that number was.
24 DOCTOR GEIS: Any GI event that was
25 identified by the committee, and Doctor Silverstein

1 can speak to this in more detail, must have been
2 accompanied by information that the patient did in
3 fact have a lesion as well as clinical signs and
4 symptoms of bleeding.
5 ACTING CHAIR ABRAMSON: As I recall the
6 MUCOSA study, you have the subset of hospitalized
7 patients, 45 or whatever the number was, in the non-
8 Misoprostol group. How many comparable kinds of
9 hospitalized patients did you have for the GI
10 toxicity?
11 DOCTOR SILVERSTEIN: In fact, it wasn't --
12 didn't quite break up that way.
13 The MUCOSA trial was a trial in 8,800
14 patients, half of which took one of ten NSAIDs and
15 half of which -- and placebo. And the other group
16 took one of ten NSAIDs with Misoprostol. And then we
17 tried to define. I mean, Dennis is obviously right.
18 It's very difficult, and Larry Goldkind talked about
19 that this morning, too. It is very difficult to
20 define what is an adverse event in a patient with an
21 ulcer complication. There's no question about that.
22 In the MUCOSA trial, to stay on point,
23 there were 42 cases in the NSAID group which
24 represented about almost 1 percent. It was about .95,
25 in six months. If you annualized that, it was about

1 2 percent. A 2 percent annualized rate of one of the
2 complications as we defined it on an NSAID alone. And
3 Misoprostol reduced that to about 1 percent. It
4 halved it approximately.
5 Now, we've been debating this issue about
6 what surrogate markers are for more than a decade. It
7 was a decade ago that I was at the FDA talking about
8 how do we study this. It was actually right before
9 David Gramm came out with his studies of Misoprostol.
10 And the question was, is there an association between
11 the endoscopic lesion that you're seeing, the small
12 ulcer, with death, and one of these events? And at
13 some point you have to stop and say, wait a second.
14 Before we change the definition of the ulcer, before
15 the change the definition of the event, how do they
16 relate to each other?
17 And the interesting part of the MUCOSA
18 study, which I felt, having spent 400 or 500 hours
19 looking at all these cases personally, was that it
20 showed that Misoprostol reduced the incidence of
21 ulcers in some six month trials by about 50 percent.
22 And Misoprostol reduced the complications by about 50
23 percent. So, it was -- and actually, in the papers
24 that Dennis was referring to in The New England
25 Journal, Hawkey said, well, there is some

1 correspondence there. It looks like if you do
2 decrease ulcers, you are decreasing these clinically
3 significant events.
4 So, I think that the second issue is how
5 do we define an event. Which, may I speak to that
6 just for a moment?
7 Naurang Agrawal and Jay Goldstein, and I,
8 sat down with the knowledge we have about GI bleeding.
9 We're all about the same vintage. We're all kind of
10 getting old together, and I've been doing this for
11 about 20 -- I think I'm the senior of the three of us.
12 And Dennis has been doing this for a long time, too,
13 about how do you define these events.
14 Surely, death is the most clear cut
15 endpoint except when you realize that even in patients
16 with bleeding who die, it's very difficult to define
17 what was the cause of death. And I did a study of
18 2250 patients in 1980 which, look at that, very
19 confusing about trying to figure out exactly what the
20 cause of death was.
21 So, what we selected was three bad
22 outcomes, bleeding, perforation, and obstruction. And
23 we attempted, and Larry and I have discussed this
24 several times, to define these things in a manner such
25 that as David Graham said, you would not want your

1 relative to have this. Now, Dennis is right. You
2 could say four units of blood. You could say you have
3 to have endoscopic intervention. That you had to have
4 surgery. You can add any definitions you want. But
5 we came up with a combination of signs and symptoms in
6 laboratory data that we thought put the patient at
7 risk.
8 In an absolutely blinded matter in the
9 MUCOSA study and in a blinded matter in these studies,
10 and it's important to address this because we're going
11 to be there shortly, what we did was we did not have
12 a specific trial. And this, Larry knows, in which we
13 looked at a large number of people on Celecoxib versus
14 an NSAID and looked at complications.
15 But, what we did was we prospectively
16 said, these are the definitions. If a person has
17 this, we're going to call this a bad outcome. And
18 every case that went through the system that Steve
19 showed us this morning -- as a matter of a fact, just
20 very quickly. It was -- slide 101, please -- that
21 every case that that was pointed out to the CRO or to
22 Searle came to our little committee.
23 So, this external committee prospectively
24 defined complications. All these possible
25 complications, there were 170 of them, in fact, from

1 both trials were referred to us. We looked at every
2 single one and Jay, and Naurang, and I reviewed every
3 piece of paper on every patient, literally, and then
4 got together and adjudicated whether it was a
5 complication or not. And it was done totally blinded.
6 So, we were blinded, too. We didn't want to know what
7 study they came from, what medication they were on.
8 All we wanted to know was the facts of their
9 hospitalization or the facts of their illness.
10 And it was based on that that we came up
11 with nine adverse events in the NSAID group in the
12 control trials compared to two for Celecoxib. And
13 Doctor Goldkind reviewed these and we've discussed one
14 or two of them. But it's a rate for NSAIDs of between
15 1.3 and 1.7 percent which is very consistent with the
16 literature. And the Celecoxib data, with two cases,
17 is .2 percent. So, it's a reduction of about seven
18 times, irrespective of where that NSAID number sits,
19 you'll see it's a reduction of about seven times.
20 And finally, in the open label trial where
21 we have 5,000 patient years, there were a total of
22 nine additional events. I think it was nine. Yes, it
23 was nine. And if you take those events, it's an
24 incidence of .18.
25 So, the point is, that I think is

1 important because I don't completely agree with
2 Dennis. I think you can get really confused about the
3 term gastropathy and the different erosion criteria.
4 He knows that. I know it, too. I spent a decade of
5 my life trying to figure out ways to stop bleeding
6 with various coagulative techniques and working with
7 ultrasound. It's a field that we've been working in
8 for a long time.
9 But, I would like to call up one slide
10 which I think kind of summarizes my feeling about the
11 surrogacy. It's slide 1072, please. And it addresses
12 this question sort of head on. Which is, are ulcers
13 surrogates for these complications. This is the
14 question which is being asked in several different
15 ways.
16 Well, the first issue is, ulcers are the
17 precursor of the complication. Because some of you
18 who know that helicobacter pylori, for example, COX
19 postulates have never been met. Barry Marshall
20 swallowed helicobacter pylori. He got an acute
21 gastritis. He did not get an ulcer. And yet, there's
22 epidemiological data about the association of H.
23 pyloria and ulcers.
24 I sat on the consensus conference about
25 five years ago which looked at that.

1 But here, ulcers are the precursors of
2 what bleeds. If you have an ulcer, it's a subset of
3 that. Dennis is right. It's a ratio of 10 or 20 to
4 1 for ulcers and ulcers that bleed.
5 The second thing is the ulcers on
6 Celecoxib are not larger or more numerous than they
7 are on other NSAIDs. In fact, they're smaller and
8 more often to be single.
9 Celecoxib, I would propose, based on the
10 three things we talked about this morning, does not
11 interfere with healing. We don't have any evidence
12 that it does. The ulcer rate is clearly lower in
13 Celecoxib. It's somewhere around 4 or 5 percent
14 compared to 15 or 20 percent in the studies in which
15 it was compared in these controlled trials plus the
16 literature. So, it's a clear five times reduction in
17 the rate of ulceration.
18 The complication rate is lowered from 1
19 and a half to 2 percent to about .2 percent. And
20 that's absolutely consistent. The experience, as I
21 was reviewing this for the 45th time on the plane
22 flying here from Seattle on the weekend, it just
23 impressed me with how large the experience in fact is.
24 The open label trial is 5,000 patient years. It's a
25 huge experience. And in those 5,000 years, we found

1 nine cases.

2 Now, Larry Goldkind who did a wonderful

3 review for the FDA never suggested we missed cases.

4 He suggested perhaps we included one or two cases that

5 were hard calls. And Naurang, and Jay, and I had

6 discussions about those cases as well. So, it was

7 nine cases in 5,000 patient years for an incidence of

8 .18.

9 And finally, I would point out, if you can

10 decrease ulcers and you can decrease ulcer

11 complications, you're significantly decreasing

12 clinical disease. Because the final statistic I'll

13 give you, those of us in bleeding say that there are

14 50 to 150 bleeds for 100,000 people for a year. In

15 Seattle, with a population of a million, it's more

16 than a million now but it's more convenient when it is

17 a million, it means there are about 1,000 bleeds per

18 year. And in the United States, it means it's about

19 260,000 bleeds per year. And those of us working in

20 the field do GI bleeding know that about half of them,

21 those patients on NSAIDs. About 150,000.

22 Now, if there are 17 million people taking

23 NSAIDs and one percent of them have a complication,

24 it's 170,000. So, the numbers all jive. The numbers

25 pretty well jive. So, I would propose, based on what

1 I consider to be a large clinical experience, that
2 Celecoxib is associated with significantly fewer
3 ulcers which are the precursors of the complicated
4 ulcer. And then, as if that's not enough, we studied
5 the complications themselves and showed a dramatic
6 reduction in complications. So, I think the data is
7 strong.
8 ACTING CHAIR ABRAMSON: May I just ask for
9 one point of clarification.
10 The nine versus the two in the -- the nine
11 in the NSAIDs, those numbers are the kind of bleeds as
12 you defined that were comparable to the 40 some odd
13 bleeds that you saw in the MUCOSA trial? So, that's
14 the comparable patient subset?
15 DOCTOR SILVERSTEIN: Right. Great
16 question. In the MUCOSA trial, we had 240 patients we
17 looked at. Sixty-seven of them we said, uh oh, these
18 are patients that we would like episodes not to have
19 happened. Of the 67, 42 were on NSAIDs and 25 were on
20 mycoprostal. But those definitions were virtually
21 identical to the definitions used to generate the nine
22 and two that Doctor Goldkind showed us this morning,
23 or the nine in the open label trial. They were
24 refined and improved a bit. And we would suggest that
25 actually that Jay, who has more energy than Naurang

1 and I do, start writing a paper about trying to
2 standardize these definitions in a manner that can
3 really be studied.
4 But, yes, they were the same as the MUCOSA
5 trial.
6 ACTING CHAIR ABRAMSON: Thank you.
7 What I'd like to do now because there's so
8 much to get at, I'd like to go around the table and
9 ask people for a question or a comment and just keep
10 going around and try and get some more discussion
11 going.
12 Doctor Silverman.
13 DOCTOR SILVERMAN: My questions were
14 answered about comparatives. I think it sounds
15 reasonable. My only concern had to do with the animal
16 studies. That over long use there was increasing
17 ulcer rate. We all know the body has an amazing
18 capacity to compensate for knocking out one arm
19 whether it be cytokines, whether it be anything else.
20 And I wonder about the long term safety.
21 The patient years are all -- 5,000, but they're all
22 short term. I mean, they're just something to stick
23 in the back of them. While the short term data is
24 convincing, I wonder whether the body may compensate
25 and we may see ulcers late.

1 DOCTOR NEEDLEMAN: In fact, the pre-
2 clinical question first. There was no sign -- You
3 want to quickly comment about that, Peter?
4 DOCTOR ISAKSON: Yes. I'd like to clarify
5 the question because I think what you said was in the
6 longer term exposure, we have more ulcers or something
7 like -- was that the --
8 Well, actually what happened in those
9 experiments or those trials, and you need to
10 understand, is that they went on for six months to two
11 years. And the exposures there, just to clarify, were
12 clearly in excess of what is therapeutic. And there
13 was not any -- not an increase with time. In fact,
14 there were occasional events, they were actually quite
15 sporadic and rare, that occurred essentially linearly
16 over time which is similar to what happens in the
17 human situation. So, it didn't -- it wasn't something
18 that came up after a long period of time but rather,
19 occurred later on. And that was only in the rodents.
20 In the dark study, actually we carried,
21 again, depending on what you use the exposure ratio,
22 six to eight-fold is therapeutic. And in that
23 situation, again, we saw no evidence of GI toxicity
24 whatsoever after a year of exposure.
25 DOCTOR SILVERMAN: Maybe my memory is

1 wrong but I thought it was 1.3 in the rodent models at
2 two years. Now, I am getting old.
3 ACTING CHAIR ABRAMSON: That was in the
4 toxicology studies.
5 DOCTOR ISAKSON: We're not sure where the
6 numbers are -- we have a little bit of
7 misunderstanding. We just need to talk to the FDA
8 about exactly what their numbers mean versus what we--
9 how we calculated the exposure multiples. But there's
10 clearly an exposure multiple in both the rodent and
11 the dog over what's therapeutic. And again,
12 contrasting that with a non-steroidal where the
13 exposure multiple would actually be a decimal, you
14 couldn't do that study.
15 DOCTOR YANG: Actually, in the two year
16 study in the mice, the GI lesion occurred, progressed
17 in time. And then because of the severe GI
18 toxicities, in the high dose they had to terminate.
19 And then for the not observed as an adverse effect
20 level, actually these are less than one times of human
21 exposure, as calculated by the AUZ 0 to 24 hour.
22 DOCTOR NEEDLEMAN: We have some both
23 animal data and then we'll follow with human data on
24 chronic exposure.
25 DOCTOR DELAP: I think if I might just add

1 something to that. And you can correct me if I'm
2 wrong. My understanding is that the animals are
3 inherently fairly susceptible to GI toxicity from
4 these kinds of products. So, when you're doing these
5 tox studies, of course, you're always pushing the dose
6 to see what dose you give to get the toxic result.
7 And in fact, the dose was pushed here and the animals
8 actually were dosed with substantially higher relative
9 doses of this product than they would have been able
10 to withstand with other kinds of conventional NSAID
11 products.
12 So, although you can say qualitatively
13 some of the lesions that were seen were the same, the
14 dose was pushed and the duration was pushed relative
15 to what the animals could have tolerated with some of
16 the other products.
17 DOCTOR ISAKSON: We'll skip the slide.
18 DOCTOR NEEDLEMAN: We agree. We'd like to
19 talk about the clinical data.
20 Steve.
21 DOCTOR GEIS: Yes, we were interested in
22 the possibility that should an event occur, do they
23 suddenly occur later on with lots of exposure. And
24 so, we took the data from the open label trial and
25 then did a Kaplan-Meyer plot of it.

1 And, if I could have that slide. You can
2 see that the -- that it really -- you don't suddenly
3 see a big jump off with later exposure. You see sort
4 of just sort of the smooth trend. Which is, I think,
5 Fred Silverstein could comment, was pretty much what
6 you saw -- you see with the MUCOSA trial.
7 DOCTOR SILVERSTEIN: Yes, you may recall,
8 Steve showed the Kaplan-Meyer curve for the MUCOSA
9 trial this morning and it showed the same thing.
10 Because it's a very important issue, this issue about
11 adaptation, does the risk go away. And perhaps one of
12 the best studies is by John Corrotta who showed over
13 a three or four year period using aspirin, a couple of
14 aspirin a day, for cardiovascular prophylaxis, the
15 risk remained relatively steady from month to month
16 for gastric or duodenal event.
17 But Steve's right. There was not a
18 tendency for all this to occur suddenly at month five.
19 The number of people who have been followed for more
20 than a year are about 2,500 and many people have been
21 followed now for 18 months on Celecoxib. So, the
22 experience continues to grow.
23 ACTING CHAIR ABRAMSON: Doctor McCarthy.
24 DOCTOR McCARTHY: This is very difficult.
25 I feel I am swimming against the tide here. But let

1 me come back to Doctor Geis' first slide that started
2 off with adverse events and then the next slide was
3 headed ulcer complications.
4 First of all, many of the bleeds are not
5 ulcer complications. Studies by Lannis and
6 Hershkowitz have shown that only in about 60 percent
7 of endoscopies can one identify a lesion in the case
8 of an upper GI bleed from an NSAID or aspirin. So,
9 where the bleed is coming from is not clear.
10 Secondly, very often we see erosions but
11 we don't actually see a cause of a clinically
12 significant bleed. And, when we find a big ulcer and
13 it is bleeding with the ratio that Doctor Silverstein
14 agrees to, it's about 20 to 1 between lesion
15 prevalence and complication prevalence, we don't know
16 whether the big ulcer which bleeds started off as a
17 peptic ulcer and was caused to bleed by the NSAID or
18 it started off as an NSAID ulcer and then bled.
19 Now, perhaps both occur. I'm not saying
20 it's one or the other. But the point is, we do not
21 know quantitatively what is the contribution of
22 previous peptic ulcer disease to the major serious
23 adverse outcomes. And I would point out that in the
24 ones in this brochure, about half of the cases who had
25 serious adverse outcomes had in fact a pre-existing

1 history of peptic ulcer disease or indigestion, or
2 something suggesting a pre-morbid condition.
3 So, we have to separate out the risk of
4 bleeding from the risk of a deterioration in an ulcer.
5 And to come back to the outcomes MUCOSA study, the
6 therapeutic gain between the treatment group who got
7 Misoprostol and the untreated group was 18 bleeders,
8 47 with a total amount. The difference between
9 placebo and treated was about 18. And there were six
10 perforations.
11 And the perforations are much more
12 reliably linked to NSAIDs than the bleeds because we
13 don't know exactly what the cause of bleeding was in
14 the 18 patients who bled. We know in a few of them
15 but they weren't all the same and they weren't all
16 endoscoped at the time of the bleed, et cetera.
17 So, we don't know where all that bleeding
18 came from. I'm not saying that Celecoxib won't help
19 in this regard because I think the anti-platelet
20 benefits of the drugs will be considerable. But those
21 benefits will apply to other drugs which are being
22 tested right now and are already on the market. And
23 I think there is, for instance, the rate of 0.2
24 percent which is quoted here is not very different
25 from the rate that Doctor Palmer presented here in

1 March for Relafin (phonetic) and similar rates exist
2 for Etodolac, for Miloxicam (phonetic), for Nimesalyte
3 (phonetic).
4 Now, we could argue about this all day
5 because not all of the studies are in. But the point
6 is that they're in the same ball park for serious
7 adverse outcomes and we don't know what's really going
8 on in that regard. So, I don't think we should
9 dismiss peptic ulcer disease, helicobacter, co-use of
10 aspirin and all these other issues at this point in
11 time.
12 ACTING CHAIR ABRAMSON: Thank you. Doctor
13 McCarthy, can we take that and we'll come back around
14 if we need -- as we need to.
15 But, Doctor McConnell.
16 Ms. Malone.
17 Doctor Harris.
18 DOCTOR HARRIS: Again, with respect to
19 treatments, there are three questions here that you
20 are being asked.
21 ACTING CHAIR ABRAMSON: I think the core
22 question ultimately will be the endoscopic -- well, we
23 should at least focus now on the value of the
24 endoscopic findings as surrogates and the relationship
25 between the clinical outcomes and the data that we

1 have. And then we can come back and fill in the other
2 pieces.
3 Or, you can ask -- or, anything that you'd
4 like to.
5 DOCTOR HARRIS: I have nothing more to
6 add.
7 DOCTOR FERNANDEZ-MADRID: I am of the view
8 that the endoscopic studies cannot be viewed as a
9 surrogate series. And from the data that was
10 presented, I am not convinced that the data has power
11 enough to determine differences in terms of
12 seriousness.
13 ACTING CHAIR ABRAMSON: Doctor Lovell.
14 DOCTOR LOVELL: Well, I think we're being
15 -- I think as to the question about endoscopy
16 surrogate -- studies being surrogates, is actually
17 better placed in question 4. And I think question 3
18 is somewhat confusing. If you extract that first
19 statement from question 3, then really the question
20 is, how do you word the labeling? Is it so that the
21 current studies will be generalized to apply to all
22 NSAIDs about endoscopic defined ulcerations? And
23 then, question 4 has to do with actually the surrogate
24 business and the serious adverse events, and that sort
25 of thing.

1 So, I would suggest that we look at
2 question 3 and strike out that first sentence because
3 it's kind of confusing the picture here. At least for
4 this question. It's more pertinent to question 4.
5 ACTING CHAIR ABRAMSON: Do you want to
6 comment on --
7 DOCTOR LOVELL: Well, as I read the label
8 this morning, I felt like the wording in the current
9 proposed label accurately and fairly specifically
10 defines the data that you have presented today. And
11 there wasn't an effort to generalize it to all NSAIDs.
12 If one wanted to be a little more expansive in the
13 comments in the label, then you could put in
14 information about kind of the frequency of ulcerations
15 seen in published studies about in other NSAIDs. And
16 there seems to be some consensus about how frequently
17 that occurs and it seems to be fairly generalizable
18 from one to the next.
19 So, that would be may suggestion if you
20 wanted to be more expansive in the label. But it
21 seems to me that the data that's in the label as it
22 stands now is informative and accurate for what was
23 shown in this study.
24 ACTING CHAIR ABRAMSON: I had thought last
25 time we met in March that endoscopy was not going to

1 be a reasonable surrogate. But I must say that it
2 seems like we have some fairly powerful data, large
3 numbers of patients. What concerns me about
4 reproducing clinical studies, and I just throw this
5 out, I don't know how we can ethically reproduce the
6 MUCOSA trial. Because to treat 10,000 people to get
7 50 bleeds, which is really the major adverse event,
8 because of the MUCOSA trial you can't do that study,
9 because everyone is now on Misoprostol or Prolisec
10 (phonetic), or something else. I raise that as a
11 point.
12 And I think we may have to decide, look at
13 whether endoscopic end points actually can be used as
14 surrogates. And there it becomes the power of the
15 data. But, I guess the question I would have, I don't
16 recall the numbers -- I may have asked this morning.
17 I'm not sure I got the right answers. Is the numbers
18 of people endoscoped at three months versus six
19 months, if we are going to use that as surrogates, I'd
20 like to know what the patient populations were. I
21 guess Doctor Geis would be in the best position to
22 answer this. How many people did you actually follow
23 for three months and endoscope? How people did you
24 follow for six months and endoscope?
25 DOCTOR GEIS: In none of the clinical

1 trials where we used endoscopy. So, for example, let
2 me simplify it. The six month study, there was just
3 an end of study endoscopy. There could have been
4 scopes early on for cause or for early withdrawal. We
5 can pull those numbers and really actually show those.
6 And in the three month studies, again,
7 they were done -- the endoscopies were at baseline and
8 then at three months. So, we don't have in a given
9 study scopes at baseline, three months, six months.
10 ACTING CHAIR ABRAMSON: I guess what I'm
11 asking, though, in the six month study, and what was
12 the end patients?
13 DOCTOR GEIS: Oh, there was approximately
14 200 patients per treatment group who participated and
15 underwent the endoscopy.
16 ACTING CHAIR ABRAMSON: At six months.
17 And at three months?
18 DOCTOR GEIS: I'll have to check those
19 numbers and bring those forward.
20 ACTING CHAIR ABRAMSON: Doctor Tilley.
21 I'm sorry?
22 DOCTOR NEEDLEMAN: The answer is
23 thousands.
24 ACTING CHAIR ABRAMSON: 4,000 patients?
25 So, 4,000 people were studied for at least three

1 months?

2 DOCTOR GOLDKIND: Those were the numbers

3 that were randomized. But the number of patients that

4 underwent endoscopy would be smaller than that and

5 then the serial endoscopy studies. So, the --

6 certainly it's over 1,000. Somewhere between 1,000

7 and 2,000 in the Celecoxib group that underwent

8 endoscopic evaluation at some point. And a little

9 under 1,500 in the active comparators. So, that's the

10 universe of endoscopic data.

11 ACTING CHAIR ABRAMSON: But, if one were

12 to try to put a minimum number of months of treatment

13 to get some clinical relevance to those endoscopic

14 studies. So, endoscopy is of very little value, I

15 think, most people agree.

16 When you get out six months, I think there

17 begins to be more validity as a surrogate end point

18 and probably at three months. And this is just an

19 opinion. How many of those couple of thousand were

20 done at three months? Was it several thousand that

21 had three months duration of therapy?

22 DOCTOR GOLDKIND: The numbers that I gave

23 you, I believe, are at the end of study, not the

24 endoscopy for cause.

25 DOCTOR GEIS: Correct. That's what we

1 had.

2 But I would like to point out that our
3 experience in doing endoscopic trials indicates that
4 when you're doing endoscopies, usually three months
5 gives you -- you reach steady state in terms of
6 incidence of ulcers. And we can show Doctor Agarwal's
7 publication several years ago. And this, again, was
8 a cytotech study and patients underwent serial
9 endoscopies for one year. And we found at three
10 months, that's when you really didn't see any
11 additional change in rate of ulceration beyond three
12 months. So, that's what caused us to believe three
13 months really is adequate when you're using ulcer as
14 your end point.

15 ACTING CHAIR ABRAMSON: And your rate was
16 approximately 4 to 8 percent, is that the range as I
17 recall? What was the --

18 DOCTOR GEIS: So, in the placebo group, it
19 was about 4 percent. And with Celecoxib it was also
20 in the range of 4 percent. Whereas, with NSAIDs, we
21 routinely at about three months were up in the range
22 of 20 to 25 percent.

23 DOCTOR GOLDKIND: There was a difference
24 between 12 week in the placebo controlled study, 12
25 week versus final, the analysis and see in the review

1 in the sponsor's data, the tables were taken from the
2 sponsor's data, differentiate. And the 4 percent
3 would be the 12 week endoscopy which was mentioned.
4 If endoscopies for cause are included, which would
5 increase the denominator in terms of the number of
6 endoscopies performed, and if an ulcer was found, that
7 would increase the numerator as well.
8 If that data is looked at, then the slide
9 that I have shown, the 2 versus 4 percent, is what's
10 shown in the results. If we were to look at the
11 combining the studies the way the sponsor has at 12
12 weeks, then it comes out to be roughly 4 versus 6
13 percent, if we look at 12 weeks as that end point as
14 opposed to trying to ascertain all ulcers in the
15 interval. So, there is a difference between but the
16 difference is a smaller percentage of the total if one
17 looks at the 12 week versus the final total, crude
18 total, however one wishes to describe that.
19 ACTING CHAIR ABRAMSON: This might be an
20 appropriate time to ask the question. There were some
21 differences in the way the data seemed to be presented
22 this morning. When Doctor Geis presented, it appeared
23 that there was no -- there were similar rates of
24 ulceration, endoscopic ulceration, in the Celecoxib
25 groups as there were in placebo. Which then makes

1 moot other comparative NSAIDs.

2 Whereas, Doctor Goldkind, I think in your

3 report, said that they couldn't show that they were.

4 the same as placebo.

5 DOCTOR GOLDKIND: The main point was that

6 the studies weren't powered to identify a difference,

7 or for that matter, to define equivalence, powered to

8 define equivalence. Doctor Witter and I kind of

9 approached from different angles -- were the sponsor

10 wish to find itself its equivalent, what would be

11 required?

12 The flip side is if one wishes to define

13 a meaningful and statistical difference, how would one

14 do it. And in all the studies, the ulcer rate was

15 above the -- the ulcer rate for the Celecoxib in each

16 dose in the two studies was higher than in the placebo

17 group. The confidence intervals were wide, although

18 the absolute difference was fairly small.

19 And on the slide that I showed of the 2

20 versus 4 percent, was simply that that came close to

21 statistical significance in differentiating even

22 though the study was not powered to look at that. I

23 think that would be my caution in interpreting the

24 data. If one does not design a study powered

25 appropriately to look for whatever a specified

1 difference may be, you may not get -- and that was
2 really -- the purpose of my points on adverse events.
3 What the sponsor did was collect data on
4 adverse events but it was not a -- there was no
5 overriding statistical plan to compare adverse events
6 to -- in each of the groups, active comparator, or,
7 for that matter, placebo. And one must really
8 approach that subject with caution, particularly in
9 dealing with a new molecular entity. And we're
10 working with the -- we're fighting over the concept
11 but is this an NSAID and therefore the issue of
12 comparability to prior studies is raised. Should we
13 be looking at prior data in the medical literature as
14 our comparator to reinforce our confidence in this
15 data, and thereby obviate the need for independent
16 study.
17 ACTING CHAIR ABRAMSON: Doctor Geis.
18 DOCTOR GEIS: Yes, I'd like to just sort
19 of show just a couple slides to clarify why there was
20 this difference in this incidence of ulcers.
21 And, I think that what I want to point out
22 is the two studies where we had placebo, those were
23 conducted, one in a -- in patients with rheumatoid
24 arthritis flare and one in patients with
25 osteoarthritis flare. Once they were randomized, they

1 were allowed to drop from the study if whatever
2 treatment they were getting did not adequately control
3 the arthritis.
4 So, as expected, the placebos were
5 dropping out much earlier than in the active treatment
6 groups. And that's reflected on a slide that I think
7 we have that is a Kaplan-Meyer plot on the percent of
8 patients who were withdrawing. And this is from the
9 022 study where we looked at placebo and Celecoxib up
10 to as high as 400 milligrams twice a day.
11 And as you can see, this is the percent of
12 patients who are remaining in the study. And the
13 placebos are in fact, as expected, dropping out early.
14 But when they dropped, we endoscoped them. But many
15 of these patients, if you endoscope -- Could I have
16 the slide back, please. If we endoscope a patient who
17 has dropped out at 14 days, and that patient does not
18 have an ulcer, is it fair to say that over three
19 months that patient would not have an ulcer?
20 So, we said for the early withdrawals who
21 did not have ulcers at their exit endoscopy, we said
22 they're basically -- it's unknown what they would have
23 had had we continued following those patients.
24 So, in our analysis, if someone withdrew
25 early and did not have an ulcer at that time, they

1 were taken out of both numerator and the denominator.
2 And that's how we came up with our numbers such that
3 we talk about it as known outcomes was our analysis.
4 And as, again, as expected, were more placebos
5 dropping early than there were in the active
6 treatments.
7 And we felt that was the fairest
8 assessment of the various treatments. Because then
9 you're dealing with patients who really did go the
10 full three months or actually we know they developed
11 an ulcer. That's how we came up with the 4 percent
12 with the placebo group.
13 I'd like to also just comment on we do
14 agree that we did not power the studies to show
15 equivalence of placebo. But we point out that in the
16 totality of the data that we have, we have several
17 hundred patients on placebo and Celecoxib and we did
18 do comparisons. And I think our interpretation is,
19 does the comparison allow one to make the conclusion
20 there is really no medically meaningful difference,
21 when you have this much data and these different types
22 of studies, including the ulcer data and the
23 complications.
24 DOCTOR GOLDKIND: I think, if I may speak,
25 that that's a fair question to ask the advisory

1 committee. Even if we take the 12 week data that
2 Doctor Geis presented earlier, there is a difference
3 of roughly 4 to 6 percent ulcer rate. And as I
4 mentioned during presentation, that would be obviously
5 reflected on a very large population in the future.
6 Is that a meaningful difference?
7 We are -- If we accept surrogacy, now we
8 have to decide what percentage difference in rate of
9 surrogate do we accept as meaningful or meaningfully
10 different? And it is a very hard question and I think
11 a point for the advisory committee.
12 ACTING CHAIR ABRAMSON: I think, if
13 possible, we'd like to get back to question 3 and see
14 if we can bring that to closure. Just a few
15 additional questions.
16 DOCTOR McCARTHY: Can I just ask Doctor
17 Goldkind, if in this study there's any evidence of
18 surrogacy? It seems to me that the data you presented
19 which looks at all of the serious adverse outcomes
20 effects, comparing Celecoxib to comparator Ibuprofen,
21 Diclofenac, and Naproxen, essentially shows very
22 little difference between Celecoxib and the comparator
23 drug in terms of major serious outcome effects.
24 My position is that I accept completely
25 the data showing the benefits to endoscopic lesions,

1 but that that is irrelevant to the clinical situation
2 that we're faced with in most cases. And that the
3 number of serious adverse events here with the
4 comparator drug also is very low. And that there is
5 no clear cut, major, distinction between Celecoxib and
6 those products.
7 DOCTOR NEEDLEMAN: * and I think you have
8 to take the numerator and denominator.
9 ACTING CHAIR ABRAMSON: Let Doctor
10 Goldkind respond and then we'll come back over here.
11 DOCTOR GOLDKIND: I think the issue is
12 that it is a very low number of total events. The
13 number of patients exposed to each drug is different.
14 And so, the absolute numbers in and of themselves
15 aren't meaningful. On the other hand, I think for an
16 issue of such import, the fact that we are dealing
17 with a very small number of events needs to be taken
18 into account and generalizability based on comparisons
19 to other studies. And the MUCOSA trial has very broad
20 shoulders today in terms of being our reference point
21 for the surrogacy.
22 DOCTOR McCARTHY: Right. But the MUCOSA
23 trial took, essentially, a low risk population. In
24 fact, the incidence of really bad adverse effects in
25 both the placebo group and the treated group was very

1 low.

2 Now, that's not the real world, again.
3 What we don't know is what are the data that would
4 have come out of exposure to the drug in a high risk
5 population that includes the elderly, those with co-
6 morbid conditions, polypharmacy, co-use of aspirin, et
7 cetera, et cetera. And that's where there's a big
8 gap.

9 So, in order to power the study, in order
10 to get a clear answer, we have to be willing to do the
11 studies in more high risk populations. And then we
12 can get some meaningful data in smaller numbers of
13 patients.

14 DOCTOR SILVERSTEIN: Just a couple of
15 quick comments, Dennis.

16 The MUCOSA study was done in patients
17 across the spectrum. And it included a bunch of
18 people with a history of ulcers and a history of ulcer
19 bleeds. So, they, in fact, were not -- you had
20 mentioned earlier they were excluded. They in fact
21 were not excluded. They were permitted on the study.
22 And there was no control endoscopy done, so as with
23 the six month rheumatoid arthritis study presented
24 this morning, patients came in the way they are
25 treated clinically.

1 And two other quick comments. To Doctor
2 Goldkind's comment. 1.68 was the incidence of
3 complications in the control trial on NSAIDs for the
4 period of time that we followed, 1.68 percent. Which
5 is the FDA said 2 to 4 percent for symptomatic ulcers
6 or complications. The ARAMIS data is 1.5 percent
7 approximately. I mean, it's spot on. The MUCOSA data
8 was 1.8 percent. It was right there.
9 And then when we looked at the Celecoxib
10 group, it was .2 percent. So, it went from 1.68 to
11 .2. With the cases that you -- you drop out, Larry.
12 You went from about 1.3 to .2. So, I think it is
13 actually -- because these differences are the critical
14 differences. It's 17 or 10 million people times 1
15 percent is 100,000 people. So, this has been the
16 conundrum in this whole field that we've had trouble
17 handling for the last couple of decades, is that it is
18 -- Dennis is right. It's a small number of people,
19 small percent. But, when you take that over the huge
20 number of people exposed, it becomes a large number.
21 And one final comment. If these studies
22 had not been done at the therapeutic doses, I would
23 say the data is very difficult to interpret. But I
24 would suggest that in fact, if we look just for a
25 moment at slide 87, just for a second. I want to show

1 you what I mean. Because I am so skeptical about
2 studies in which drugs are described at low doses and
3 when a dose creep occurs, all of a sudden you're
4 finding other results.
5 I would show you that the studies of
6 Celecoxib included doses up to 400 milligrams twice a
7 day and showed the same incidence of ulcer disease.
8 So, I think this important information that the dose
9 that's going to be used therapeutically is the dose
10 that was studied endoscopically.
11 And, Doctor Abramson, I agree with you.
12 I don't know how we're going to insist on a 10,000
13 patients studied for every new approach to this
14 problem. And I think it's much more -- this is the
15 issue we've been dealing with for decades. It's much
16 more traceable if you can find an acceptable surrogate
17 marker that permits studies to be done of doses and
18 duration, and helicobacter pylori without each one of
19 them requiring a 10,000 person study.
20 ACTING CHAIR ABRAMSON: Let me ask one
21 final question and then we'll go around the room and
22 then ask people's opinions. But I'd like to ask of
23 both the sponsor and of Doctor Goldkind, and first to
24 the sponsor. Have you not kind of answered this
25 question of endoscopy as a surrogate marker? Isn't

1 that what you're really saying. You have endoscopy
2 data and then you have clinical data of 1.68 percent
3 and .2 percent. You've got nine PUDs versus two PUDs.
4 Have you not really done the studies that have begun
5 to show this is a surrogate marker?
6 That's for both the FDA and for Searle.
7 But, is the data not there to answer this question?
8 DOCTOR GEIS: I think definitely it is.
9 That's why we collected it. That's why we went
10 through an extraordinary amount of energy in those 14
11 studies and in the open label trial to collect
12 meticulously any possible cases of GI complication.
13 Systematically put it through an external committee
14 that was blinded to the patients, blinded to their
15 treatment, blinded to the study, to really make -- to
16 collect that information so that we could match the
17 ulcer complication data with all the ulcer data that
18 we worked. And it really did come out and create the
19 picture that we think is -- tells the story.
20 ACTING CHAIR ABRAMSON: Doctor Goldkind?
21 DOCTOR DELAP: I was just consulting
22 there.
23 I think our attitude is that the data that
24 are provided are certainly interesting. The numbers
25 are small but they're -- they contribute.

1 But again, if I could come back. I think
2 in question 3 we're simply asking what should the
3 sponsor be allowed to say in labeling about endoscopy
4 studies. And that's reducing question 3 to sort of
5 the bottom line. So, the possible answers are the
6 most conservative. You say nothing until you've
7 definitively proven clinical significance, or you
8 could say you could report the studies that have shown
9 a reproducible advantage over another product in terms
10 of ulcer rate designed by endoscopy. Or, you could
11 say we think we should include all endoscopy studies
12 in the labeling.
13 It does relate to some degree on how
14 persuasive you think endoscopy is as a clinically
15 meaningful end point. So, do you think it might
16 surrogate or not? If you clearly thought there is no
17 way it's a surrogate, then you probably say well, it's
18 just irrelevant information.
19 But if you think it might be a surrogate,
20 then you might say that it's fair that company should
21 be able to report it. And then you have to go back to
22 -- you have to show reproducible advantage over
23 another product. They may have to just have done one
24 study.
25 So, those are some of the issues. But

1 again, if we could -- I think we just got the sense of
2 the committee as to whether the endoscopy studies
3 should be reported.
4 DOCTOR LOVELL: Let me speak to that
5 issue.
6 I think it's, as I reflect on the
7 knowledge of medical risk and labor intensive effort
8 goes into over 4,000 endoscopies. Some of these poor
9 patients had four and five endoscopies through the
10 course of the trial. I think this is a very large
11 amount of data. And I think it would be foolish to
12 not report that information in the label. I mean, I
13 think you wouldn't want to throw that data away.
14 It's an enormous amount of data that we
15 have that we don't generally have when we look at
16 NSAIDs. And so, I think that we should well put it in
17 the label. It's already put in the label in some
18 wording. And so, I think we ought to address the
19 question specifically as you request, is how do you
20 put that information in the label? How would you
21 think it would be most appropriate or fair? And I
22 think that's what question 3 relates to and is quite
23 independent of the surrogate issue, I think. It's
24 really, if you like to put it in there, how do you
25 think it's fair to put it in there.

1 I wish we'd move ahead and vote on that
2 one because we've got more questions later that I
3 think are even more important that this one.
4 DOCTOR NEEDLEMAN: May I, just before you
5 vote. It is really quite important, the context, I
6 guess there's two issues. We work closely with the
7 agency, in fact even in the design. So we took on
8 doing zero, one, two, and three month serial endoscopy
9 carrying both positive and negative controls to reach
10 that end point even though we felt that scientifically
11 if we did it at zero time at the end point with
12 positive and negative controls, that that would be a
13 clear case. And during those trials, we showed dose
14 dependency and time dependency, and about an eight-
15 fold differential from NSAIDs, and something you can't
16 distinguish from placebo.
17 Now, if you begin to calculate what it
18 takes to get statistical difference, to show that
19 there is no statistical difference, you might require
20 a trial of 40,000 or more patients. That's a
21 different kind of an event completely.
22 So, part I was the whole mentality of the
23 design was the surrogate of the serial endoscopy.
24 Secondly, it's still how you get to a bleed if you
25 didn't have the initial primary event. And this is a

1 surrogate of the actual event. It's quite unlike even
2 tracking cholesterol and going to myocardial
3 infarction. This was a precursor of the actual event.
4 And so, in the continue of that with the
5 MUCOSA, with the backtracking of 4,000 and then more
6 patients in the open label trial, we really think that
7 that was the surrogate and the expectation with which
8 we sought out and worked together with the agency for
9 years in that desire.
10 ACTING CHAIR ABRAMSON: What I'm going to
11 do, this is what I'm going to do. We're going to go
12 around the table and make final comments on this issue
13 and everyone gets a chance to say what they think
14 about this, and then we're going to vote. And just
15 begin with how compelling is the evidence in endoscopy
16 and the clinical relevance of it which will effect the
17 label.
18 DOCTOR PUCINO: I think the labeling
19 should reflect what the actual studies show. And I
20 would not vote that you blanket -- that you have a
21 better effect in all NSAIDs. But, there is good,
22 convincing data that there is some benefit here and
23 state it as such.
24 DOCTOR TILLEY: I agree.
25 ACTING CHAIR ABRAMSON: I would agree that

1 the label clearly has to -- should reflect the
2 specific studies that were done. I guess the larger
3 issue is that I'm -- there is compelling data that's
4 been presented, both endoscopically which is borne out
5 by the clinical adverse events, that I think shows
6 that the drug is fairly comparable to placebo. And
7 that obviates the need to match it against every other
8 NSAID out there because I think it is in the class
9 with the NSAIDs. And I think the data on other NSAIDs
10 is fairly -- is quite clean. That is, the incidence
11 of ulcers is significantly higher than what we're
12 seeing with this drug.
13 So, I would like to see the data but also
14 some comment along those lines.
15 DOCTOR LOVELL: I agree. No further
16 comment.
17 DOCTOR FERNANDEZ-MADRID: I agree we
18 should include the data. And I feel that the label
19 should be conservative. I think conservative is the
20 best I can say.
21 ACTING CHAIR ABRAMSON: Doctor Harris.
22 DOCTOR TILLEY: I just want to say that I
23 would tend to follow the FDA point of view about the
24 accountability, very cautious in how you refer to
25 that. Because I don't think you've shown a

1 equivalence to placebo. And I think they haven't
2 shown a difference. But that's not the same thing.
3 ACTING CHAIR ABRAMSON: Doctor Harris.
4 DOCTOR HARRIS: I feel exactly the same
5 way. That the data should be reported exactly as
6 stated.
7 MS. MALONE: I agree with that.
8 DOCTOR McCONNELL: I agree.
9 ACTING CHAIR ABRAMSON: Doctor McCarthy.
10 DOCTOR McCARTHY: On the subject of
11 agreeing to show the data as stated, I think the word
12 endoscopic should precede ulcers in all issues related
13 to labeling and that it should carry no implication
14 that this is a surrogate.
15 And to come back to the point last made by
16 the previous speaker, if something is occurring in one
17 in 20 cases who have the lesion, how do we know the
18 lesion is the surrogate as against peptic ulcer which
19 occurs with the prevalence of about 10 percent in the
20 population at risk.
21 So, I think any notion of surrogacy should
22 be avoided. The labeling should be conservative. And
23 I think that short of an outcome study on the
24 clinically relevant end points, I would not be happy
25 with any implication that this drug is going to have

1 a marked reduction in peptic ulcer complications.

2 ACTING CHAIR ABRAMSON: Doctor Silverman.

3 DOCTOR SILVERMAN: I agree with everything

4 said. Just that equivalent shouldn't be mentioned.

5 I think that they're very similar but four in six

6 aren't equivalent and the confidence intervals show

7 that they may not be so. As long as you say very

8 similar but not equivalent, sounds like a good idea.

9 ACTING CHAIR ABRAMSON: All right. So, we

10 will come back and I think address the issue of

11 labeling in the GI warning which we're going to go

12 back to some of the points that were made here.

13 We'll take a 15 minute break and come back

14 at 10 after 4:00.

15 (Whereupon, the foregoing matter went off

16 the record at 3:58 p.m. and back on the record at 4:15

17 p.m.)

18 ACTING CHAIR ABRAMSON: We will try and

19 address the next series of questions.

20 DOCTOR NEEDLEMAN: Mr. Chairman.

21 ACTING CHAIR ABRAMSON: Yes. Yes sir.

22 DOCTOR NEEDLEMAN: While you're settling

23 in the chair, could we just try a little bit of a --

24 not a statistical discussion but kind of what are the

25 public health implications of what we were just

1 talking about. And I'd like to ask Gerry Faich if he
2 would. And he's from University of Pennsylvania. And
3 might just give you in a minute a bit of perspective.
4 ACTING CHAIR ABRAMSON: Okay.
5 DOCTOR FAICH: Thank you very much.
6 My epidemiologic perspective, having
7 looked at the open label trial as well as the case
8 control studies of upper GI bleeding relating to non-
9 steroidal use, goes something like this. And all I'm
10 doing is restating some of the data you've heard. But
11 I think it might be helpful to think of it in these
12 terms.
13 The background rate of ulcer
14 complications, meaning GI bleeding, obstruction, and
15 perforation in the general population, is on the
16 order, as you've heard, of .2 percent. A better way,
17 I believe, to think about that is two per thousand
18 person years. That's the background rate.
19 The non-steroidal rate of ulcer
20 complications per thousand person years of exposure at
21 OA doses is on the order of 20 per thousand person
22 years. That's the 2 percent you've heard of before.
23 And the difference between those, of course, is 18 per
24 thousand person years. That 18 is what contributes to
25 the 160,000 hospitalizations and the like. And I

1 think the way to interpret the elimination or the
2 marked reduction by using Celecoxib of GI bleeding or
3 GI complications from non-steroidal use is to think
4 about the 18 per thousand.
5 To my sense, is that that differential has
6 gotten lost here. The other implication of those
7 numbers using a denominator of 1,000 person years is
8 the 024 study which to my mind is a very large study
9 with 5,000 person years, tells you that the expected
10 number of leads if those patients were on usual OA
11 doses of non-steroidals, would be 20 times 5, would be
12 100. And indeed, on the order of 9 we're seeing
13 during that period. That again tells you that the
14 reduction is on the order of nearly ten fold, or
15 looked at another way, something on the order of 90 GI
16 bleeds and perforations were prevented over those
17 5,000 person years.
18 The other, and last, implication is in
19 those terms you begin to, as you well know, appreciate
20 how difficult it would be to construct a clinical
21 trial based on showing equivalency for clinical events
22 to placebo because you would need an enormously large
23 study.
24 So, I think my final point again is that
25 what we're talking about here is a differential or a

1 savings on the order or the -- reducing an
2 attributable risk of 18 per thousand upper GI bleeding
3 complications and ulcer complications.
4 ACTING CHAIR ABRAMSON: Thank you. I
5 think the consensus of the committee was that the
6 endoscopic studies were valuable but proof still
7 remains in these clinical kind of data. And trying to
8 get a handle on the validity of those data is, I
9 think, the essence of what we're trying to get done.
10 We've had a request for Doctor Singh to
11 make a very brief two minute presentation.
12 Doctor Singh.
13 DOCTOR SINGH: Thank you very much. I'm
14 going to time myself so I don't exceed two minutes.
15 ACTING CHAIR ABRAMSON: We'll time you.
16 DOCTOR SINGH: I direct the ARAMIS post-
17 marketing surveillance program. And that's where a
18 lot of the data that you've been seeing on the
19 epidemiology of NSAID gastropathy comes from.
20 And just sort of to put things into
21 perspective, we now have followed almost 76,000
22 patient years. So, just putting numbers into
23 perspective. And we've evaluated now over 700 serious
24 GI events of which at least 300 of them were serious
25 GI hospitalizations with complications such as

1 clinically significant bleeding that put patients in
2 a hospital and killed patients.
3 So, looking at those numbers and then you
4 are looking at when we are arguing that five, or six,
5 or seven, or eight, or nine bleeds as to what they
6 mean in clinical surrogates.
7 I wanted to make two comments in here.
8 One was what Doctor McCarthy was saying. That it is
9 indeed true that when you see frank cases of GI bleed,
10 and we're not talking about an occasional black stool.
11 I'm talking about hematemesis, melena hemoglobin
12 dropping to 4 grams, patient in the hospital with
13 shock, dying of it. You cannot -- in half the
14 patients, 40 percent of the patients, and I just
15 finished reviewing the last 100 cases over the
16 Thanksgiving holidays, you cannot document an ulcer.
17 So, the bleeding is occurring but you cannot document
18 an ulcer.
19 Now, having said that, it's probably also
20 likely that Celecoxib, because of its effects or lack
21 of effects on the platelets, would also reduce those
22 complications. But the fact that this whole concept
23 that if there is not an ulcer, where is the bleeding
24 coming from is not true. And that is, I think, the
25 most important part as you're going to the surrogacy

1 arguments in here.

2 And the second thing I think is a point

3 that, Steve, you've already brought up. Is that in

4 terms of interpreting outcome data -- I'm getting

5 about five seconds in their warning. In terms of

6 interpreting outcome data, we -- when we start looking

7 at the .2 percent rate in the general population, we

8 have very tight confidence intervals because we have

9 several thousand patients.

10 So, again, this studies that are designed

11 for comparison cannot often be used for equivalency

12 and should not be taken in the bulk of the data.

13 Thank you very much. I'm done with my

14 comments.

15 ACTING CHAIR ABRAMSON: Thank you very

16 much.

17 I think we're going to move, really, to

18 the core of question 4 which Doctor Lovell had alluded

19 to before. And that is, should the qualifications be

20 made to the NSAID GI warning template while noting the

21 limited experience with the new molecular entity.

22 And I'd like to ask if any of the panel

23 members would like to make initial comments?

24 Ms. Malone.

25 MS. MALONE: The one question I have is --

1 this has a lot to do with the press that's been going
2 out. This is being asked to be approved as an NSAID.
3 They're not trying to have it considered as a new
4 class of drug.
5 ACTING CHAIR ABRAMSON: Can we ask the
6 agency that? Is that a request or something we should
7 comment on?
8 DOCTOR DELAP: Well, I think we look at
9 each drug based on its individual merits. The drug
10 does share some features with NSAIDs. I think that's
11 why the question is here. We think that it does have
12 effects on postulating synthesis. They are, perhaps,
13 somewhat different than the other drugs that have been
14 traditionally called NSAIDs.
15 So, I guess the best way to put it is,
16 it's at least sort of an NSAID. And the question is,
17 how much do we think it really is the same versus how
18 much do we think we can distinguish it. And that's
19 what question 4 is getting at.
20 For purposes -- the default position is
21 always to say, well, you've got a warning. You have
22 to put up with that unless you can that it's not
23 necessary. Or that it can be -- you have data that
24 can be modified in some way that is medically
25 meaningful. So the default position would be to

1 include it saying that, yes, this is an NSAID and this
2 warning is included. However, what we're asking here
3 is whether in looking at the data that you've seen,
4 you think some modification is appropriate.
5 ACTING CHAIR ABRAMSON: How does that
6 effect what you're thinking of?
7 MS. MALONE: Well, no, it's just that in
8 the application that the way I read it from the drug
9 company is they were calling it an NSAID.
10 DOCTOR NEEDLEMAN: No, I don't think
11 that's correct.
12 MS. MALONE: Or it's not?
13 DOCTOR NEEDLEMAN: I think that was not
14 our intention. We really think that we could
15 discriminate by mechanism.
16 MS. MALONE: All right. Could you repeat
17 that last part.
18 DOCTOR NEEDLEMAN: We really think that
19 the characteristics of the molecule, its mechanism,
20 its targeting, and its sparing, really warrants a
21 separation from NSAIDs. And so, that was the intent
22 of our submission and the magnitude of the trial. We
23 could have done a trial one-tenth the size if we were
24 going to submit for an NSAID indication.
25 MS. MALONE: Well, then, this could be a

1 semantic thing. But if you're not considering it an
2 NSAID, you wouldn't compare it to other NSAIDs. You
3 would say, in comparison to NSAID.
4 DOCTOR NEEDLEMAN: We are looking at a
5 standard of care. It is the dilemma when you're
6 departing in a whole new direction than what exists.
7 And when you do a trial, you want to include positive
8 and negative control based in the disease entity. In
9 our trials in -- other trials in Alzheimer's there
10 will be different kind of comparatives and not anti-
11 arthritic. So, based on the mechanism and the
12 existing standard of care, that was the basis of the
13 trial.
14 But we really -- our intention and
15 proposal is specific COX-2 inhibitors for the
16 treatment of osteoarthritis, rheumatoid arthritis, and
17 the management of pain.
18 MS. MALONE: Well, I'm just trying to
19 understand it as a consumer, what class of drugs it
20 is. If it is something new, then essentially there's
21 nothing just like it that you can compare it to.
22 DOCTOR NEEDLEMAN: That's correct. This
23 is the first drug in this class of specific COX-2
24 inhibitors that has gotten this far for consideration.
25 ACTING CHAIR ABRAMSON: Doctor Silverman.

1 DOCTOR SILVERMAN: Question. Is it
2 specific or very selective that you're actually asking
3 for?
4 ACTING CHAIR ABRAMSON: Is this a COX-2
5 specific drug or selective? How do you want to define
6 that?
7 DOCTOR NEEDLEMAN: We could -- that is an
8 interesting semantic discussion. We chose specific
9 because selective, there has to be implications about-
10 - and we talked about it before. There was a correct
11 discussions of other drugs that wanted to claim some
12 level of selectivity but in fact that wasn't
13 therapeutically or medically meaningful. So, we
14 thought embedded in specific also describes its unique
15 properties in the clinical and the pre-clinical.
16 One could argue, if you said highly
17 specific and set a number, that would be a
18 differential. So, you might be able to say an agent
19 is 3X or 10X specific. You would never be able to do
20 the dog trials. They would all be dead. You would
21 have GI events. You would have platelet reactions.
22 So, we chose specific COX-2 inhibitors as the class.
23 ACTING CHAIR ABRAMSON: Let's, because of
24 the time, focus on the GI warning issue. And I think
25 that it's presumed that as least for this discussion,

1 that as we go forward, the drug is going to have an
2 NSAID GI warning, potentially, except as we discuss it
3 right now as to how relevant we think that continues
4 to be. And the issue of whether it's an NSAID or not,
5 I guess is very relevant to whether it carries an
6 NSAID warning label.
7 But I think we should talk about -- I
8 guess, should we discuss is this an NSAID or is this
9 a separate class of drugs? Or, do we have to have
10 that discussion?
11 DOCTOR DELAP: I'm not sure how productive
12 that is.
13 ACTING CHAIR ABRAMSON: So, let's -- So,
14 if we don't -- I guess the reason I'm getting there,
15 if we don't, then we're going forward as though it
16 were an NSAID carrying this label. And the question
17 is, should this label not apply to this drug.
18 DOCTOR DELAP: I mean, if all you have to
19 do is develop a new product and say it's not an NSAID,
20 then you don't have to have the NSAID warning, then I
21 can tell you what kind of implications we're going to
22 get down the road.
23 ACTING CHAIR ABRAMSON: So, for the sake
24 of this discussion, whatever we call this, should the
25 NSAID GI warning be carried on this drug?

1 DOCTOR LOVELL: If I may comment.
2 Certainly this drug is not ulcer- free. I don't think
3 anybody would want to advocate that patients who take
4 this drug are not going to develop ulcers, or they
5 won't develop ulcers. Certainly patients in your
6 trial did. But I think that some warning in the label
7 should reflect the fact that ulcers can occur. And
8 when I was reading through the label information, the
9 standard class labeling for NSAIDs includes
10 quantitative information that's not accurate for
11 what's been shown for this drug in terms of 1 percent,
12 2 percent, that sort of thing.
13 So, I think that the class labeling should
14 be included, but should be revised so that it reflects
15 the -- information should be added to reflect what new
16 information we have about this product that's somewhat
17 different than the standard observations in the other
18 NSAIDs. And so, that's what I would suggest.
19 If you just put in the information that we
20 just said we're going to include in label 3, and then
21 put in a standard class label for NSAID, it's
22 confusing to the reader to say well, here's this
23 information but then there's other information. How
24 does it apply to this particular product. So, I would
25 think you would have to meld the two so that the label

1 is informative of the situation as we understand it at
2 this point in time.
3 ACTING CHAIR ABRAMSON: That was listed as
4 an option by Doctor Witter, as I recall. There's a
5 modification for an extended label.
6 Any other comments?
7 Doctor Fernandez-Madrid.
8 DOCTOR FERNANDEZ-MADRID: I would agree.
9 I have nothing to add to it.
10 ACTING CHAIR ABRAMSON: Why don't we just
11 go around.
12 DOCTOR HARRIS: Well, I guess I would
13 agree. But I think some statement in terms of the
14 modification, it seems to me, I'm still not convinced
15 that sufficient studies have been -- at least we've
16 observed these agents for long enough, really, to say
17 too much different from what is currently there, the
18 NSAID label.
19 I guess one can start saying this is the
20 data. And also indicate this is this stage, and
21 pending for this study is maybe a little different.
22 I don't know if you understand that. But certainly
23 I'm not convinced as yet, my own view, that this is
24 going to be here, in the end, differently from NSAID.
25 I think we need some more studies.

1 ACTING CHAIR ABRAMSON: What kind of
2 studies would you recommend?
3 DOCTOR HARRIS: Well, if not more studies,
4 at least let me say along the Phase IV period. I
5 mean, I really would hesitate to ask them to go back
6 and do really long, very expensive, sorts of studies
7 again. But certainly I feel that for myself, I'd like
8 to see more time with these agents before removing
9 what is the current NSAID.
10 ACTING CHAIR ABRAMSON: Ms. Malone.
11 Doctor McConnell.
12 DOCTOR McCONNELL: I would agree, we need
13 -- it is an NSAID that, after all while you're hearing
14 what it does. And I think modification is
15 appropriate. The risk of ulcers is not zero but does
16 seem to be something less.
17 ACTING CHAIR ABRAMSON: Doctor McCarthy.
18 DOCTOR McCARTHY: I would be very careful
19 to not regard tox-selectivity, in other words, a
20 mechanism of action, as a criterion for creating a
21 class of drugs. Because when all said and done, there
22 are a putative 20 mechanisms or so right now for non-
23 steroidal injury including effects on free radical
24 formation, ischemia, all sorts of things.
25 And this is a very slippery slope. If we

1 start saying that COX selectivity is a criterion for
2 a different type of licensure, we're going to get into
3 a very grey zone about what ratio constitutes
4 selectivity, in what assay systems over what period of
5 time, over what dose range, et cetera. And we have
6 already in the literature from the very large studies
7 of Garcia, Rodriguez, and Jigg (phonetic) that have
8 looked at a database of two million people with 33,000
9 complications. Evidence that the relative risk for a
10 really bad adverse outcome is product specific.
11 Now, I agree with Doctor Silverstein that
12 it's also effected by dose and that's an additional
13 factor. But it is product specific. And if we look
14 at the selectivity ratios, they are fairly predictive
15 across the board of the relative risk of a serious
16 adverse outcome. But there are some notable
17 exceptions. And for instance, if we look at the
18 ratios for Etodolac and Nebumetone (phonetic) are six,
19 seven, eight, we find that right between those is
20 Ketorolac, which is probably the most dangerous drug
21 on the U.S. market. And it has a relevant risk of
22 24.7 for oral use and a very high rate of perforation
23 and ulceration in even five days of parenterotherapy.
24 And yet, on COX selectivity alone it doesn't look too
25 bad.

1 And just because we have defined one new
2 mechanism of injury, which I agree with, it doesn't
3 mean that all of the other things that we've learned
4 about in the past including biliary excretion, protein
5 binding carboxylation, et cetera, et cetera, are all
6 irrelevant.
7 So, I think this is a slippery slope and
8 that we should not make COX selectivity on its own a
9 basis for a new claim for either safety or efficacy.
10 ACTING CHAIR ABRAMSON: I think that's
11 very important and it's got to be organ system based
12 toxicity that we look at in clinical trials.
13 Doctor Silverman.
14 DOCTOR SILVERMAN: I agree that just a
15 modification to the standard GI would be appropriate
16 to reflect the numbers. But that the elimination of
17 this as an NSAID, currently I don't think the data
18 supports that.
19 ACTING CHAIR ABRAMSON: Doctor Pucino.
20 DOCTOR PUCINO: Yes. Modification of the
21 GI label.
22 DOCTOR TILLEY: I agree.
23 ACTING CHAIR ABRAMSON: I would agree with
24 modification to reflect the data that we have. I --
25 the question was raised about more data, whether more

1 studies are appropriate or not. And I guess that
2 depends on whether one believes that the current data
3 are sufficiently compelling to show a significant
4 decrease in clinical outcomes. We put the endoscopic
5 studies aside.
6 Though here's the -- Doctor Needleman.
7 DOCTOR NEEDLEMAN: We would like to
8 comment.
9 I have to wonder what it's going to take
10 to depart from traditional therapy for a brand new
11 mechanism. If we look at the ICH guidelines, if we
12 wanted to do an NSAID, all we had to do was 15,000
13 patients. We did nearly ten times more patients and
14 dissected every organ system and every newly expressed
15 organ system that expressed COX-2 that even had a
16 potential for its side effects beyond the initial
17 hypothesis. The depth of the data, the extent of the
18 endoscopies, and all of the other systems in fact is
19 really designed -- and look at all of the -- If you're
20 going to say non-steroid, look -- You're going to be
21 seeing the inhibitors or the usable nitric oxide
22 synthase. You're going to be seeing matrix
23 metalloproteases.
24 There's a whole new world of drugs that
25 are going to be coming. And if -- we're going to end

1 up with NSAID and at the end of doing 13,000 or
2 14,000, and then saying you better do another 10,000
3 or 15,000, it really precludes the design. And now
4 we're going after chronic diseases which really effect
5 the quality of life, and they're going to have a
6 design that's going to have to be tracked for years.
7 So, it's very, very different than if you
8 come part of the way and say it's modifying the GI
9 warning but it's quite different than if you said, for
10 this stage of the data you have a COX-2/NSAID.
11 Now, if you really want to get it
12 completely changed, then there's another kind of phase
13 IV trial, then, you might suggest. But the reality of
14 the practicality of moving forward after such an
15 extensive trial, and there's a lot of precedent for
16 calling drugs by their mechanism of action. We have
17 angiotensar receptor blockers. We have ACE
18 inhibitors. We have HMG co-A reductase inhibitors.
19 So, here is, now, a targeted drug, a smart
20 drug, that's direct specifically at the site and it's
21 sparing a whole level of side effects. So, we would
22 argue that it's not a matter of bigger trials because
23 this is the biggest kind of trial that's ever been
24 done in arthritis, and it's purpose was to move that
25 class label and to be recognized in the labeling.

1 You know, the -- Our job, and it is
2 correct, to pick apart each piece of data because each
3 patient is an important event, it's pretty interesting
4 as we've shared this data in meetings and peer review.
5 The fact of the matter is, the concept of COX-2
6 inhibition and the aggregate of the drug fits the
7 hypothesis. The reduced GI safety. The reduced
8 endoscopy. The effects on platelets. And where we
9 agree with the renal assessment.
10 And it really looks like the differential
11 and renal might have reflected that standard NSAIDs
12 were powerful COX-2 inhibitors and were powerful COX-1
13 inhibitors. Millions of patients have had COX-2
14 inhibition. Some of that side effect at the level of
15 renal were probably indeed part of COX-2. Not the
16 renal capillary necrosis, not the other parts, but the
17 transient natriuresis is clear.
18 So, I would articulate that there will be
19 many, many people coming forth with these agents. And
20 it's not with the mentality that we wanted another
21 NSAID. You've had NSAIDs for two decades and haven't
22 been able to discriminate. You've had dosage creep.
23 And you start with a low dose and get a positive
24 endoscopy, and then in the real practice you get to a
25 dose and you'll get endoscopic and you get GI events

1 and hospitalization.

2 So, I would argue that the database is

3 adequate and it's not just the GI side effects but the

4 class label that we're here to discuss.

5 ACTING CHAIR ABRAMSON: I think the -- we

6 need to discuss both of these things. I think the

7 class label is where we begin in terms of the data

8 that's been presented in terms of GI toxicity.

9 Because I think one could debate back and forth

10 mechanisms of action. And then that ultimately these

11 curves tend to converge and you get COX-2 inhibition

12 and COX-1 inhibition. And since the mechanism of most

13 NSAIDs is by COX-2 inhibition in terms of the

14 therapeutic effect.

15 One could argue the other side about

16 whether or not this is working by a different

17 mechanism based action.

18 I think to me, and we see that in the

19 renal profiles, that it really looks like an NSAID in

20 the renal profile. So, I must -- the selective issue,

21 I think is an important conceptual one. But I think

22 it really comes down to the robustness of the data

23 largely in the GI tract. And I think that's where we

24 really have to spend a lot of time and we have spent

25 time but it's the core issue.

1 And, as I said before, I am very impressed
2 with both the endoscopic and the clinical data that
3 you have, whether you call this an NSAID or anything
4 else. And the question is, how do we discuss that
5 issue with respect to the class label. How many more
6 patients can you possibly study and get better data?
7 And I think this really has to be where this
8 discussion is about the class label.
9 And we have differences of opinion.
10 Doctor Goldkind in his analysis felt that we weren't
11 able to show absolutely that this was not as safe as
12 a placebo and that ulcers did occur. And then once
13 you say ulcers can occur, then you're looking at the
14 class label and the class label simply says ulcers can
15 occur. And I think that's where we're having this
16 dilemma.
17 I frankly think that these drugs are safer
18 than the current drugs that we've seen. But their
19 mechanism of action is similar. So, when we talk
20 about the label, we really have to ask, do we accept
21 the robustness of the data? Do we need more studies
22 at higher doses which some people have articulated?
23 And I think that's the core issue today. And I think
24 that's what the panel is going to have to vote on.
25 We've expressed some opinions about what this drug

1 looks like in terms of what the label might show.

2 Ideally, if it was purely data driven, the

3 label would only show what the data allows us -- would

4 warrant. And ideally, therefore, one might not need

5 a class label as such. But I think that's were this

6 debate has to be, not over whether a COX-2, in my

7 mind, a COX-2 selective drug is really different from

8 the other NSAIDs based on its mechanism of action.

9 So, where do we pick that up? How strong

10 and compelling are the GI data, the .2 versus 1.68?

11 DOCTOR DELAP: I would say, I think I did

12 hear kind of an emerging consensus amongst -- as you

13 were polling the members. I thought the class label

14 was still important but also that there was a

15 necessity for some modification to reflect the data

16 about the endoscopic findings. And so, I think that's

17 what I've heard so far.

18 I would like just to digress slightly in

19 saying that Doctor Needleman and colleagues are

20 absolutely correct, that they could have done a much

21 smaller package if they just wanted to develop this as

22 an "NSAID." And they have done a lot of additional

23 studies that would not ordinarily be required. And I

24 would say that at different times and different

25 settings I've heard people, both inside and outside

1 the agency, express their pleasure in seeing so much
2 good clinical data and such a thoughtful effort in
3 trying to set out this COX-2 business.
4 So, I think they deserve a lot of credit
5 for it and they deserve some things in the labeling
6 that other people without the same data would not get.
7 And I think we heard what you said before, that the
8 studies that have been done be reflected in the
9 labeling.
10 And again, just to come to closure on
11 question 4, I guess, what I heard from your polling
12 the committee was that people seem to think that class
13 warning couldn't be lifted particularly but it needs
14 to be modified.
15 DOCTOR TILLEY: I wasn't saying that. I
16 thought the question I was answering was the wording
17 of the label and whether it could be modified to
18 address this new drug. So, I really wasn't making a
19 judgment about whether it should or should be called
20 an NSAID.
21 I guess my one concern about calling it an
22 NSAID is it doesn't have the same platelet activity.
23 And that, just by calling it an NSAID, might be
24 misleading for someone who is expecting this to be
25 both. That's a question -- I'm not a physician. I'm

1 a bio-statistician, but that's something that concerns
2 me a little bit.
3 DOCTOR LOVELL: May I make a comment?
4 I viewed question 4 in somewhat a
5 pedestrian and pragmatic fashion. And that is, how do
6 you make the label be informative for the reader? And
7 that was, as indicated this morning, the role of the
8 label is to try to inform in an accurate fashion those
9 who would be prescribing the drugs.
10 And, my comments were placed on the table
11 in that mind set. Is, yes, the way the class label
12 reads now, it's misleading or doesn't provide complete
13 information about how this drug has differentiated
14 itself from other NSAIDs.
15 Now, that's a somewhat different question,
16 I think, than the more, perhaps, broader question of
17 whether this drug should be considered as an entirely
18 new class. And I think that's a somewhat different
19 question. And my comments were actually about the
20 label per se. And I think question 4 is perhaps in
21 that mind set also.
22 I think it's an entirely different
23 question, a much broader question, a much broader
24 question, as to whether this drug merits being placed
25 in an entirely new class and incorporates a number of

1 issues other than the labeling information.

2 ACTING CHAIR ABRAMSON: Doctor Silverman.

3 DOCTOR SILVERMAN: If I can just look at

4 the label in two places. One is initially what talks

5 about clinical pharmacology and mechanism of action.

6 It appears that there should be some direct statement

7 of the -- I don't like the word specificity, so I

8 would call high selectivity of COX-2 inhibition over

9 COX-1 inhibition, which addresses the concern. And

10 then you -- But it still could be labeled as non-

11 steroidal. But every time with the recommendation --

12 the addendum, I guess is the word, of a higher

13 selectivity for COX-2 inhibition.

14 And that may be the compromise that will

15 address the issues because the physician hopefully

16 will recognize the difference and it could be spelled

17 out in the label as it will, I'm sure, regarding

18 platelets, et cetera, what the difference between COX-

19 1 and COX-2 inhibition of that reflex.

20 ACTING CHAIR ABRAMSON: Doctor Fernandez-

21 Madrid.

22 DOCTOR FERNANDEZ-MADRID: I think this is

23 going to be a very good drug. I think this is going

24 to be an improvement on other non-steroidals that are

25 in use at the present time. But it seems to me that

1 historically it is premature to create a new class of
2 these compounds. If we look initially COX-1. Then we
3 have COX-2. And now we have an inhibitor that is
4 called specific or selective, or highly selective.
5 And what this means is it inhibits COX-2 but it does
6 not inhibit COX-1.
7 But from the literature or some of the
8 studies that we heard today, these molecules does
9 things in addition to inhibiting COX-2. I think some
10 of the side effects may be present not by inhibition
11 of COX-2 but for some other unknown reason. It's
12 likely that we will discover that these molecules,
13 these "class of molecules" will do other things in
14 addition to inhibiting COX-2.
15 And the picture that I am seeing at the
16 present time is not quite different from the non-
17 steroidal, although it is much improved. It does
18 still perforate the stomach. It still people bleed.
19 Still people die from this although much less than
20 before. I think there is a critical difference than
21 we have recognized. That it is an improvement in the
22 platelet program is very significant that we have some
23 other non-steroidal, like salicylate, that does
24 something similar to it.
25 We have renal effects which are very

1 similar to these. So, in generally, it seems to me
2 that this falls within the spectrum of non-steroidal
3 at the present time although it is promising to be a
4 very much improved drug. I would maintain the
5 expectation.
6 ACTING CHAIR ABRAMSON: So, let's just
7 bring this piece to closure and divide it into two
8 things.
9 One, we -- a recommendation will be that
10 the label include all of the specific data, including
11 the decrease of the clinical relevant events and the
12 fact that this class -- this COX-2 -- so this is the
13 first highly selective COX-2 inhibitor that will not
14 have platelet effects.
15 That's a proposal. I think -- I'd just
16 like to get a sense of the committee on the vote. If
17 the label obviously and the class warning will include
18 that. So, anyone in favor of that addition?
19 (Whereupon, a show of hands.)
20 ACTING CHAIR ABRAMSON: Anyone opposed to
21 that qualification?
22 (Whereupon, a show of hands.)
23 ACTING CHAIR ABRAMSON: And the second
24 question is whether the notion that this class label
25 as it currently exists be taken out of the -- that we

1 not have the class label for this drug with the
2 caveats based on data from other drugs of the NSAID
3 class. We just need to address that as a specific
4 issue.
5 I'd like to see if anyone wants to make
6 additional comments to address some of these.
7 Doctor Harris
8 DOCTOR HARRIS: Can I just -- in terms of
9 the class label, in terms of risk of GI ulceration,
10 bleeding, and perforation, in other words, the
11 statement would still read that like other non-
12 steroidals, there is a significant risk similar to
13 others. Because this is the first sentence of the
14 warning that's there. And once one says it's a class
15 label, presumably that sentence remains.
16 ACTING CHAIR ABRAMSON: Right. Taking
17 into account we've seen both endoscopic and clinical
18 data that suggests that the risk is much less.
19 DOCTOR McCARTHY: Can we qualify that by
20 saying that the risk of hemorrhage and of endoscopic
21 ulcers appears less but there is absolutely no data on
22 perforation. And that the animal studies at least
23 indicate a potential for an increase in perforation if
24 conventional peptic ulcer disease or other lesions are
25 caused to deteriorate by these compounds, particularly

1 in patients with pre-existing disease.

2 ACTING CHAIR ABRAMSON: Is that -- do we

3 have data on perforation?

4 DOCTOR NEEDLEMAN: Are you talking about

5 pre-clinical data or are you talking about --

6 DOCTOR McCARTHY: Yes. The pre-clinical

7 data are significant. And they're enough to raise a

8 warning that we should not assume that perforation of

9 clinical ulcers will diminish. And I say this because

10 in the severe adverse effects that Lawrence Goldkind

11 has in the report, most of the patients who had really

12 bad effects had a previous history of peptic ulcer

13 disease or pre-existing indigestion.

14 So, there is a possibility that those who

15 have helicobacter or other related peptic ulcer

16 disease may perforate.

17 DOCTOR NEEDLEMAN: May we divide this into

18 two parts and first go through the pre-clinical data.

19 Peter or Tom. I don't know where

20 perforations concepts is even coming from in pre-

21 clinical.

22 DOCTOR McCARTHY: Perforation is coming

23 from published research papers by independent

24 investigators who have shown in animal studies that

25 the class COX-2 selective inhibitors inhibits ulcer

1 healing and studies from Gretzer in Germany have shown
2 a significant dose related effect on perforation of
3 the small intestine with Celecoxib.
4 DOCTOR NEEDLEMAN: Doctor Delap, maybe you
5 could give us guidance. Our data, chronic exposure to
6 animals at multiples of the human therapeutic dose,
7 don't have any of these events that are being
8 described with someone else's data. Should we go
9 ahead and go through that data again, or do we --
10 DOCTOR DELAP: I'm not sure that we
11 actually need to have that level of detail in the
12 committee's recommendations, actually. I think that's
13 something you can work out with the company. I would
14 only note that unless I'm mistaken, I don't believe
15 there were any perforations in this database on
16 Celecoxib. Am I correct?
17 DOCTOR NEEDLEMAN: That's correct.
18 DOCTOR DELAP: Clinical.
19 DOCTOR NEEDLEMAN: That's correct.
20 DOCTOR SILVERSTEIN: Yes, in fact, that's
21 exactly correct. And I would just note, again, that
22 over 2,400 patients have been followed on Celecoxib
23 for a year and during that period of time there have
24 been no perforations. And the comparable data from
25 the MUCOSA trial was in six months in 4,400 patients.

1 There were -- or, in the 8,800 patients there were ten
2 perforations.
3 DOCTOR DELAP: I would just say that based
4 on your comments, we'll just re-examine it with the
5 company, make sure that we got it right.
6 DOCTOR McCARTHY: All I'm saying is that
7 I think there is more need for caution about
8 perforation which is a less common event. It's about
9 one-fifth as common as bleeding.
10 ACTING CHAIR ABRAMSON: I think -- Let me
11 -- It's late but this is the most important issue of
12 the day in many ways. So, I want to just raise this
13 one more time and open up a question which is to say,
14 if we don't change this class label, then the sponsor
15 would be asked to do another additional clinical
16 trial.
17 And I think that's the decision -- I mean,
18 that's one of the issues that we really have to
19 confront. And the question, therefore, is can another
20 large clinical trial be done? How robust this data
21 is, and how much more we need. And I think that even
22 though it's late, I think that's a very core issue
23 right here. And I'd like people to talk about it a
24 little bit.
25 DOCTOR LOVELL: Well, let me ask you.

1 What clinical trial are you talking about? What point
2 do they have to establish?
3 ACTING CHAIR ABRAMSON: Well, let's go
4 back. We put that class label in four years ago
5 because of the epidemiologic -- the clinical outcome
6 base. That is, everyone said endoscopic data is not
7 an adequate surrogate for clinical outcomes and says
8 they're dangerous.
9 And now we have to make a decision that
10 class label was put in there because of clinical
11 outcomes. And now a company is coming and saying we
12 have new data. Is it sufficient to strip away that
13 label that came as a result of ARAMIS and other
14 databases. And we have to make the judgment as based
15 on the endoscopic data and the clinical data, have
16 they met that bar? Have they gotten to the level
17 where we can say no, that doesn't apply to you? And
18 that, I think, is the central issue. Whether you call
19 this a different class drug or not.
20 And so, if we don't accept that data, then
21 the question is, what data is feasible to get beyond
22 that. And given the MUCOSA study and the fact that we
23 have to cover people who are high risk with antacid
24 prilosec, what is the scope of that study. And I just
25 -- we need to flush that out to make this decision

1 about class label.

2 DOCTOR LOVELL: So, if I understand your

3 point, it's if the company can establish that they

4 don't have the ulcer risk, then that would be

5 sufficient information to justify creating a new class

6 of drugs being the COX-2 inhibitors or whatever you

7 call it.

8 ACTING CHAIR ABRAMSON: I'm sorry. When

9 I say -- I'm using two terms. The class label is the

10 NSAID warning for the GI class label, I apologize.

11 It's not the NSAID class.

12 DOCTOR LOVELL: Well, I think the bigger

13 question, and the request here, is that they be viewed

14 as an entirely new class of drug which I think is a

15 much broader issue than just a GI --

16 ACTING CHAIR ABRAMSON: Right. I want to

17 focus just on the class label for the moment. That's

18 the question 4. Do we keep in the class label? We

19 suggested at least modifying it based on the data.

20 Now the question is, do they deserve a class label for

21 GI toxicity, not whether they're an NSAID or not? And

22 I just want to open the discussion up.

23 DOCTOR DELAP: Can I just amplify a little

24 bit on what the current view is at the company. I

25 think the company is planning to do some further

1 studies to further -- Even though they've already done
2 a lot of studies, there are some further plans that
3 they have to do some additional studies. One of the
4 other impetuses, or impeti, I'm not sure what the word
5 is, for class labeling, of course, was kind of
6 accumulated experience over the years and spontaneous
7 reports, and this sort of thing.
8 So, part of it, I think, is answered by
9 just what comes in after a product is marketed.
10 Obviously after a product gets on the market, we get
11 a lot of additional information from the spontaneous
12 adverse reporting system and the company is tracking
13 that. We're tracking that. And that helps a lot.
14 Because even with thousands and thousands of patients,
15 when it's on the market, it's millions and millions of
16 patients. And we learn a lot more.
17 So, part of it is the formal additional
18 studies the company may be willing to do, and part of
19 it is simply what happens after the product is
20 marketed. It can help a lot.
21 DOCTOR NEEDLEMAN: Of course, a large
22 trial is something you do kicking and screaming. And
23 the reality is, it's accruing more of the same data we
24 have. And if there's not some recognition like
25 removal of the NSAID class label or some incentive to

1 do such a large trial, then there's the ethics of
2 exposing tens of thousands of patients to the point
3 that you get an ulcer and a perforation, or an
4 obstruction.
5 So, there is the two parts, I agree. One
6 is the removal of the class label of NSAID. Two, what
7 do you have to do to change the class? If the first
8 doesn't come into place, it's hardly reasonable to
9 push all those patients to that level of risk to
10 accomplish the second. What's the good of saying
11 specific COX-2 inhibitors if you haven't removed the
12 NSAID class label.
13 ACTING CHAIR ABRAMSON: Let me ask, what
14 would be -- where would be the bar for the GI class --
15 the GI toxicity label to be removed from this drug?
16 DOCTOR DELAP: It's difficult to give a
17 crystal clear answer to that because there are
18 different pieces to the information that are provided
19 in the class warning. And some of them -- there are
20 some issues that still remain with a COX-2 selective
21 drug and some issues that might go away. So, it's
22 hard to say definitively what pieces.
23 What I would say is that our usual
24 approach in these kinds of situations is to sit down
25 with the company and say okay, if you do this

1 additional study, this is potentially your gain if the
2 study works out the way you like it to work out. And
3 we know how important this is to the company and it's
4 something that we have discussed, naturally we
5 continue to discuss with them. What additional
6 studies there might be versus what further labeling
7 changes we think that might support.
8 Again, I think the charge today is to say,
9 well, what's on the table today in terms of data, and
10 what can we do with it. Then as we look at further
11 studies down the road and what we might be able to do
12 with those as far as further enhancements of the label
13 for the company, that is it gets into exactly what the
14 study is and what the results are. And typically
15 we'll try to involve the advisory committee members
16 when we think about those issues, and certainly
17 involve you when we come to the end of those kinds of
18 studies.
19 So, that's kind of a long winded answer
20 but I think the bottom line is today what we need to
21 settle before we leave the room is what do we think
22 they should get, at least fundamentally, from the
23 studies that have been done. And the -- I would say
24 that can there come a time when there's no longer a
25 need for a class label for a product that actually

1 clearly has a clinical profile, that's different, or
2 to create a different class label for a product that's
3 clearly different. Well of course there is. It's
4 just a little hard to be more specific about how the
5 pieces have to fit together.
6 But, again, I think to date there's been
7 a lot of good work done and the intention is that, to
8 the extent possible, to the extent that it's helpful
9 for prescriber and patient as that's reflected in the
10 labeling. And there is -- these things can be
11 resolved in the future.
12 The simplest thing would be if you did a
13 big study and you showed that there was just clearly
14 improved equivalence of placebo on some important end
15 point like ulceration or clinical GI events. Some of
16 those kinds of studies simply cannot be done based on
17 the numbers. We have to look into other ways of
18 getting the same information reliably and
19 scientifically.
20 So, I don't want to be here saying that we
21 would set a bar impossibly high to do that. But
22 that's -- I think we could discuss that all night and
23 all day tomorrow if we wanted to figure out exactly
24 what the parameters are.
25 ACTING CHAIR ABRAMSON: Well, then may I

1 summarize --

2 DOCTOR SILVERSTEIN: I'm sorry. Doctor

3 Abramson, just two quick comments.

4 One comment I'd like to make to put this

5 in perspective a little bit because I misspoke a

6 little bit.

7 In the MUCOSA trial, we had 4,400 patients

8 on NSAIDs for six months. Ten of them had a

9 perforation. So, that's 4,400 patients in six months,

10 that's 2,200 years. Here, in 5,000 years, we've had

11 no perforations on this drug. So, just another piece

12 of looking at risk.

13 And the second question I would ask

14 because I've been doing this for about 25 years as

15 several people in the room have, I would ask, would

16 the warning even be put on in the first place with the

17 data we have on this drug? Because in 1988, we were--

18 the clinical gastroenterologists were the people

19 saying, hey, there's a problem here. A lot of the

20 bleeders we see are on these NSAIDs and on aspirin.

21 And there -- 50 percent of the people were seeing

22 bleeding. What I would ask if, it were an incidence

23 of two per thousand as opposed to 20 per thousand,

24 would we have put the warning on in the first place?

25 ACTING CHAIR ABRAMSON: I think just to

1 bring this to closure, I'd like to take a vote on just
2 that. That if this drug were coming to market before
3 the warning, would we put that warning on? And I
4 think I'd just like to have a show of hands. And so,
5 the question is, would -- to state this question,
6 sorry, it's late but these are very important issues.
7 Based on the data, should the class
8 warning remain, the class GI warning?
9 And I would -- people who think yes, class
10 GI warning should remain, should raise their hands.
11 DOCTOR NEEDLEMAN: You mean as it exists
12 without any wording changes?
13 ACTING CHAIR ABRAMSON: No with the
14 wording changes that we've suggested to reflect the
15 data. Like that it may be dangerous in the elderly --
16 DOCTOR NEEDLEMAN: It's still a little
17 unclear. You might try again.
18 DOCTOR NEEDLEMAN: I'm tired, too, and I'm
19 standing.
20 ACTING CHAIR ABRAMSON: Let's do it this
21 way. Let me make a statement what I think is the
22 sense of the committee, and then make that as a
23 recommendation to the Agency.
24 Is that I think, and -- I think most of us
25 believe that this drug has really gone a far distance

1 towards accomplishing the goals of a COX-2 selective
2 drug that one would like to see with decrease GI
3 toxicity and other safety elements, and platelet --
4 and lack of platelet effects. And it tends to have
5 renal side effects concomitant with an NSAID type
6 profile. And that the data appears to be really
7 approach a bar that ought to have removed GI safety
8 labeling. And that we would ask the Agency to look at
9 the data, carefully look at what kind of outcome
10 studies you might think you can discuss with the
11 sponsor.
12 But that this is a very close call, at
13 least in my mind, that there -- it may not be all
14 there but the data is very compelling, both endoscopic
15 and numbers of patients, clinical outcomes. And we
16 need not focus on the label but I think the sense --
17 and I want people to give me a sense whether they
18 agree with this or not, is that there's a lot here
19 that really approaches the kind of NSAID that we would
20 like to see with GI safety profile. And you need to
21 talk about where that bar has to be set and what kind
22 of additional studies need to get done.
23 Is that -- do you have a comment on that?
24 DOCTOR LOVELL: Yes, I have a comment.
25 I agree with what you said. You've also

1 answered 4, 5, and 6 all in one fell swoop. But, I
2 also think that if you just look at the words on the
3 page in the label here, and divorce yourself of
4 whether it's class labeling or not labeling, just look
5 at the words and see if they're accurate in the data
6 that exists for this particular product. A lot of
7 that wording is not accurate for what has been
8 developed through a number of clinical trials, with a
9 great deal of effort, and reflects what they do.
10 So, my suggestion is if you were editing
11 a manuscript, and just look at this as a manuscript,
12 and you were trying to edit the manuscript in a way in
13 which it would reflect the true data that's been
14 presented in this product, then you'd have to do lots
15 of editing to this manuscript to make it reflective of
16 the data that you have at hand. And so, I'm thinking
17 that the editing that would be required for the GI
18 section of this label is going to be fairly
19 significant, as is the editing that's going to have to
20 be done for the hematologic parameters of the label as
21 a result -- as it reflects other NSAIDs. Not so much
22 change for the renal stuff and that sort of thing.
23 So, that's where I stand in terms of this.
24 And I think my view on this is just reflect what data
25 we have and try and make the labels the most accurate

1 and informative that there is, and eliminate those
2 words in the current class label that don't pertain to
3 this product.
4 ACTING CHAIR ABRAMSON: Any other
5 comments?
6 Doctor Needleman.
7 DOCTOR NEEDLEMAN: You're heading in the
8 right direction.
9 ACTING CHAIR ABRAMSON: Don't you have any
10 slides so you can keep this --
11 DOCTOR NEEDLEMAN: What slides? You never
12 heard of number 2,000?
13 ACTING CHAIR ABRAMSON: All right. I
14 think we can possibly move a little more -- I think
15 this issue is the core issue. And we had to spend as
16 much time as we did.
17 DOCTOR DELAP: Yes, I think it's been a
18 wonderful discussion. I think in looking at the
19 remaining questions, my proposal would be we'd like to
20 hear comments on numbers 5 and 11. We are happy to
21 work with the company on 6 through 10, unless the
22 company wants some public discussion of those or
23 unless the committee has some issues on 6 through 10
24 that they think we need to talk about.
25 DOCTOR NEEDLEMAN: We surrender. Let's do

1 5 and 11.

2 ACTING CHAIR ABRAMSON: Question 6 is the

3 concomitant administration --

4 DOCTOR NEEDLEMAN: Five.

5 ACTING CHAIR ABRAMSON: I'm sorry.

6 Question 5, concomitant administration of prophylactic

7 aspirin. And I think it's pretty clear that if you

8 want to get the benefits of COX-1 inhibition, you're

9 going to have to, in the indicated patients, use

10 aspirin. Obviously, when you do that, you begin to

11 negate the -- a potential benefit of this to the

12 extent that low doses of aspirin may be associated

13 with GI bleed as many people believe.

14 I think you have to -- I don't -- I think

15 you have to use low dose aspirin where indicated but

16 understanding that you may counteract the effects of

17 this drug. But --

18 DOCTOR NEEDLEMAN: Can I make a small --

19 This goes back to where I was still

20 pipetting at the bench. I want to remind you about

21 the pharmacology and pharmacokinetics of aspirin.

22 Aspirin is a very labile substance and very quickly

23 broken down after ingestion. The reason it's so

24 important in cardiovascular use is that the platelets

25 lack a nucleus. So, when you use aspirin, you

1 irreversibly, covalently, and permanently inhibit the
2 platelet cyclooxygenase.
3 Any other tissue which has a nucleus, the
4 gut, the blood vessels, and everything else, are only
5 transiently blocked by aspirin. So, the reality is
6 its important use of low dose like baby aspirin is
7 that that inhibits both the platelets in the
8 megakaryocytes. So, the concept that there's a
9 potential for an overt interaction is really belied by
10 the fact that every other place beside the platelet
11 turns over cyclooxygenase and constantly makes new
12 enzymes. So, there really isn't irreversible blockage
13 at other sites. So, just as for a perspective.
14 ACTING CHAIR ABRAMSON: Right. That's an
15 important point. And also, the issue of using low
16 doses, 80 milligrams or less, which theoretically
17 don't get on to the systemic side of the circulation,
18 I think is very important here.
19 And it may be a role to look at in enteric
20 coating because you wonder whether some of the GI
21 toxicity that's been observed, even at the 80
22 milligram dose, is perhaps due to local effects.
23 DOCTOR SILVERMAN: I think on the point,
24 if there's toxicity at 80 milligrams of ASA, you would
25 not believe that this would change it in the least.

1 I mean, that's the crux, so --

2 DOCTOR NEEDLEMAN: Correct.

3 ACTING CHAIR ABRAMSON: Right.

4 DOCTOR NEEDLEMAN: Correct.

5 DOCTOR SILVERMAN: It would make it worse.

6 ACTING CHAIR ABRAMSON: Right. But

7 clearly, it's better than using a non-selected drug

8 where you're getting ulcers and bleeding even in the

9 low doses.

10 DOCTOR NEEDLEMAN: Absolutely.

11 ACTING CHAIR ABRAMSON: Any other comments

12 on this issue?

13 I'm sorry, which other points did you

14 want?

15 DOCTOR DELAP: You can skip to 11 unless

16 some member of the committee wishes to discuss one of

17 the other questions. We don't want to quash any

18 discussion but just in the interest of time, I think

19 we could work out 6 through 10, the kind of details,

20 with the company.

21 ACTING CHAIR ABRAMSON: I'm sorry, 11 is

22 what recommendations for Phase IV studies for

23 celebrex? I think we kind of alluded to the issue of

24 setting some standards for the GI toxicity that would

25 go on between the discussions between the Agency and

1 the sponsor addressing the issue of the label. But,
2 I think the comments are pretty clear from us.
3 Any additional Phase IV?
4 DOCTOR LOVELL: The pediatric question
5 comes back. So, I'd be curious to see what
6 discussions have been between the Agency and the
7 company about pediatric studies.
8 DOCTOR NEEDLEMAN: Steve or Peter.
9 DOCTOR ISAKSON: Our -- The pediatric
10 program has been relatively conservative. We carried
11 forward all the trials that you've seen to date in
12 those 18 years of age and older. But our plan is to
13 carry forward, and in fact we have a toxicology plan
14 ongoing, to dose first animals to determine for
15 certain whether there's an potential toxicity in the
16 juvenile population and the neo-natal population in
17 animal studies. If in fact that shows it would be
18 suggested to be safe, then we drop down and start
19 looking at patients, for example, juvenile rheumatoid
20 arthritis patients. And we've been in discussions
21 with the agency about exactly how to time that and how
22 to move forward in the most cautious and conservative
23 way.
24 We certainly have plans to move forward in
25 that population. But again, in a conservative way.

1 ACTING CHAIR ABRAMSON: Any other
2 comments?
3 Doctor Fernandez-Madrid.
4 DOCTOR FERNANDEZ-MADRID: The point was
5 made some hours ago that whether the data could be
6 extrapolated to all non-steroidal and you wonder if
7 the sponsor would consider to use other milder non-
8 steroidals available in the market like salicylate,
9 like enteric coated Naproxen?
10 DOCTOR NEEDLEMAN: I'm not sure we
11 understand the question. I think in a traditional
12 Phase IV, we'll do other comparatives with time. And
13 that would be an evolving issue that we would work out
14 internally with the Agency and internationally, too.
15 Because there are different comparatives in different
16 countries.
17 ACTING CHAIR ABRAMSON: And you're saying
18 to take those that are associated with fewer GI side
19 effects and look at those?
20 DOCTOR NEEDLEMAN: Yes, that would be our
21 intention.
22 ACTING CHAIR ABRAMSON: Doctor Harris.
23 DOCTOR HARRIS: And this is to ask the
24 FDA. My bar actually would be equivalence to the
25 placebo. And if -- As you collect data, I'm sure in

1 adverse GI effects, suppose a year from now there is
2 data, compelling data, suggesting equivalence to the
3 placebo. Would that be sufficient? I mean, at what
4 stage is there sufficiency to say that this is truly
5 behaving in a fashion with respect to GI toxicity, as
6 you collect more data?
7 DOCTOR DELAP: I think if we saw data that
8 clearly statistically demonstrated equivalence to
9 placebo, then we'd be delighted. I think, looking at
10 the numbers as I'm sure the company has done, it's not
11 the most practical thing in the world to accomplish
12 sometimes. But we'll -- I think we -- Again, I feel
13 good that we'll learn a lot from the post-marketing
14 data collection.
15 At some point, a product gets in the
16 market place and you start seeing what happens in
17 millions of people. And there's just no way you're
18 going to see that in the pre-marketing arena. And you
19 can get more and better data from that experience.
20 DOCTOR NEEDLEMAN: We agree with that. Of
21 course, the complexity is you can't carry placebos.
22 Placebo drop out rate, you very quickly. So, you
23 might get caught in the trap, well, here's a placebo
24 rate for three months. Should I multiply it times
25 four for a year and times eight for two? So, I think

1 tracking the adverse responses in the expanded
2 population is more realistic approach.
3 ACTING CHAIR ABRAMSON: Felix.
4 DOCTOR FERNANDEZ-MADRID: I wonder if some
5 studies on bone have been done. And if not, possible
6 they would be a candidate for some future study.
7 DOCTOR NEEDLEMAN: We haven't done such
8 studies.
9 ACTING CHAIR ABRAMSON: Any other
10 comments?
11 DOCTOR LOVELL: Actually, I have one
12 further comment about the pediatric issue. And I
13 think the reality is that when this drug gets
14 approved, and when it gets available on the market, it
15 will be given to children. Without question it will
16 be given to children with juvenile rheumatoid
17 arthritis. And my guess is if you get eventually a
18 pain indication, it will be given to children for a
19 variety of pain situations.
20 But I, with absolute confidence, know that
21 it will be given to children with juvenile rheumatoid
22 arthritis as soon as it's on the market. Independent
23 of what your studies in neo-natal mice or rats show,
24 it will very soon be given to children as soon as it
25 gets on the market. And I think neither the agency or

1 you as the company would want to be in a situation
2 where that's been done in kind of an unstructured,
3 free wheeling fashion because of the fact that it may
4 well -- clinicians' assumptions about what might be an
5 equivalent dose wouldn't necessarily be what would be
6 derived from a well designed PK safety type study.
7 So, my suggestion is that it's a euphemism
8 to say that your pediatric program has been
9 conservative when you're doing the drug with 15,000
10 adults and zero people less than 18 years of age. So,
11 I would suggest you move ahead with the pediatric
12 program in real patients very quickly in a way that's
13 going to be informative to a clinician who will be
14 giving this to children.
15 DOCTOR NEEDLEMAN: That's a point well
16 taken and we'll give it high priority. It is
17 certainly an area that we intended to go forward in.
18 ACTING CHAIR ABRAMSON: Any other
19 suggestions? That's the kind of information that you
20 were looking for?
21 DOCTOR DELAP: Yes, that's helpful. Are
22 we at the end, do you think?
23 (Laughter.)
24 I was just going to say, again, that I
25 really appreciate all the thought that's going into

1 this and the preparatory work by the Committee, and
2 the tremendous efforts the company who've done a real
3 job here unparalleled in our experience up until this
4 time. And we really appreciate it.
5 DOCTOR NEEDLEMAN: Thank you. I could
6 tell you a model of pain and that's going through this
7 all afternoon.
8 ACTING CHAIR ABRAMSON: Well, I also want
9 to thank the FDA staff and the members. And thank
10 Searle for patience in the presentation and really for
11 -- the whole story of this is very compelling and it
12 seems like the bar is almost right there.
13 DOCTOR NEEDLEMAN: Thank you.
14 (Whereupon, at 5:20 p.m., the advisory
15 committee was concluded.)
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CERTIFICATE

This is to certify that the foregoing transcript in the

matter of: ARTHRITIS ADVISORY COMMITTEE

Before: FDA/CDER

Date: DECEMBER 1, 1998

Place: SILVER SPRING, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Rebecca Davis