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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE

NDA 20-988/S009, Celebrex, (celecoxib, Searle)

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P R O C E E D I N G S

Call to Order and Introductions

HARRIS: I would like to call the session to order. My name is Nigel Harris. I am Dean and Senior Vice President for Academic Affairs at Morehouse School of Medicine and I am also a rheumatologist.

Before we do the introductions, I am going to ask Ms. Reedy to read the statement.

Meeting Statement

MS. REEDY: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions; in accordance with 18 United States Code 208(b), full waivers have been granted to Drs. Frank Harrell, Steven Nissen, Ileana Pina, M. Michael Wolfe and Allan Sampson.

Copies of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office located in Room 12A30 of the Parklawn Building.

1 We would, however, like to disclose for the record
2 that Dr. Steven Nissen, Ileana Pina, H. James Williams and
3 M. Michael Wolfe have interests which do not constitute a
4 financial interest within the meaning of 18 United States
5 Code 208(a) but which create the appearance of a conflict.

6 The agency has determined, notwithstanding these
7 interests, that the interest of the government in their
8 participation outweighs the concern that the integrity of
9 the agency's programs and operations may be questioned.
10 Therefore, Drs. Nissen, Pina, Williams and Wolfe may
11 participate in today's discussion of Celebrex.

12 With respect to FDA's invited guest expert, there
13 are reported interests which we believe should be made
14 public to allow participants to objectively evaluate his
15 comments. Dr. Byron Cryer would like to disclose that, in
16 1997, he received a research grant from Merck to conduct a
17 small clinical study on rofecoxib. He has received
18 consulting and speaker fees from G.D. Searle, Pfizer and
19 Merck for work on celecoxib and rofecoxib. Additionally, he
20 has previously been a consultant for SmithKline Beecham and
21 Ortho McNeil.

22 In the event that the discussions involve any
23 other products or firms not already on the agenda for which
24 an FDA participant has a financial interest, the
25 participants are aware of the need to exclude themselves

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1 from such involvement and their exclusion will be noted for
2 the record.

3 With respect to all participants, we ask, in the
4 interest of fairness, that they address any current or
5 previous financial involvement with any firm whose products
6 they may wish to comment upon.

7 I might add that the waiver criteria can be found
8 at the FDA's site on the Web. I won't quote the law. That
9 is too long.

10 DR. HARRIS: Thank you.

11 We can now begin with our introductions. I will
12 start on my left with Dr. Cryer. If you can give your name
13 and where you are associated

14 DR. CRYER: Byron Cryer, University of Texas,
15 Southwestern Medical School, Dallas, Texas.

16 DR. WOLFE: Michael Wolfe, Boston University
17 School of Medicine, Boston, Massachusetts.

18 DR. PINA: Ileana Pina, Case Western Reserve
19 University, Cleveland, Ohio, Cardiology.

20 DR. NISSEN: Steven Nissen, Cardiologist,
21 Cleveland Clinic, Cleveland, Ohio.

22 MS. McBRAIR: Wendy McBair, Southern New Jersey
23 Regional Arthritis Center at Virtua Health in New Jersey.

24 DR. WOFYSY: David Wofsy, University of California,
25 San Francisco, Rheumatology.

1 DR. CALLAHAN: Lee Callahan, University of North
2 Carolina, Chapel Hill, Department of Orthopedics.

3 DR. HARRIS: I repeat that I am Nigel Harris,
4 Morehouse School of Medicine, and Dean, Senior Vice
5 President for Academic Affairs. And I should add, a
6 rheumatologist.

7 MS. REEDY: Kathleen Reedy, Food and Drug
8 Administration, Advisory and Consultants Staff.

9 DR. WILLIAMS: James Williams, University of Utah,
10 Rheumatology.

11 DR. SAMPSON: Allan Sampson, Department of
12 Statistics, University of Pittsburgh and currently on
13 sabbatical as a visiting scholar, Department of Family
14 Preventive Medicine, University of California at San Diego.

15 DR. ELASHOFF: Janet Elashoff, Biostatistics,
16 Cedars-Sinai Medical Center and UCLA.

17 DR. HARRELL: Frank Harrell, Biostatistics,
18 University of Virginia School of Medicine. I am a
19 Consultant to CDER Biostatistics.

20 DR. WITTER: Jim Witter from the FDA.

21 DR. GOLDFIND: Larry Goldfind, FDA.

22 DR. BULL: Jonca Bull, FDA.

23 DR. DeLAP: Robert DeLap, FDA.

24 DR. HARRIS: Thank you.

25 We will now hear from Dr. Jonca Bull who will give

1 welcome and introduction.

2 **Welcome and Introduction**

3 DR. BULL: First of all, welcome. Thank you very
4 much to our committee for coming here this morning. Please
5 know how much we appreciate your willingness to share your
6 time and your intellect to assist us in our deliberations on
7 these important topics over the next two days.

8 Can we ever know enough about the safety of a
9 drug? Can we ever know enough about the safety of drugs
10 that have had widespread acceptance in the marketplace where
11 rare events can become numerically significant numbers.

12 We are here today as part of a continuum of
13 discussion on the safety profiles of two drugs that were
14 approved in 1999 and that have literally had, I think, one
15 of the most--as, I think, an article in USA Today asserted,
16 some of the most successful launches of drugs in U.S.
17 pharmaceutical history.

18 We ask that you deliberate carefully, think
19 broadly and, again, welcome.

20 I would like to introduce Dr. Jim Witter who will
21 be providing for you a regulatory and scientific background
22 in the issues that we will be discussing over the next two
23 days. Thank you.

24 MS. REEDY: I might comment that our podium is in
25 this position for electronic reasons. We apologize for any

at

1 inconvenience.

2 **Regulatory and Scientific Background**

3 DR. WITTER: Good morning.

4 [Slide.]

5 I would like to thank, especially the members of
6 the advisory committee, for taking time from their busy
7 schedules to be here.

8 The discussion for the next two days, then, will
9 focus primarily on the question of whether Cox-2 agents, as
10 currently recognized by the division, are safer than Cox-2
11 nonselective agents, commonly called nonsteroidal
12 antiinflammatory drugs or NSAIDs. In fact, some discussion
13 will focus on whether these Cox-2 agents were studied at 2X
14 dose and, if so, whether these superphysiologic doses are
15 safer than NSAIDs at their conventional doses.

16 To help address the various aspects of safety,
17 large and simple trials were conducted by both sponsors.
18 The division is aware that it is not often that meetings to
19 discuss issues of safety postapproval are discussions of
20 improved safety. More often, it is, in fact, the opposite.
21 So this is going to be a welcome discussion for the next two
22 days.

23 [Slide.]

24 We thought it would be useful to set this in
25 context. There is a rich history in this area and so we

1 thought a few minutes to set aside to put that in some kind
2 of--put this meeting in context would be useful.

3 As we know, acetylsalicylate, also known as
4 aspirin, was first synthesized and sold in 1899. About
5 forty years later, there was the first evidence by endoscopy
6 that this compound could damage the upper GI tract. About
7 30 years or so later, we started seeing the new safer NSAIDs
8 being developed and approved.

9 In 1992 was the first widely held idea that Cox-2
10 was discovered, that, in fact, there was yet another target
11 for these enzymes. Before that time, we thought there was
12 just a single target. In 1998, we had the first advisory
13 committee for the first Cox-2 and it was approved in that
14 year. Today, we are discussing the first large and simple
15 safety trials.

16 [Slide.]

17 The FDA has also been involved with the help of
18 the commit
19 tee, as today, for quite a while. Back in December of 1986,
20 we discussed the databases that went into the formulation of
21 the GI paragraph. In October of 1995, there was a series of
22 two-day meetings where we discussed the revision of the
23 NSAID class label and also had a citizen petition for the
24 removal of peroxicam from the marketplace.

25 In March of 1998, we had, before the approval of

1 any of these compounds, a meeting to discuss some of the
2 safety issues that we felt were emerging with these
3 particular compounds. As said before, in December of 1998,
4 we had the advisory committee for Celebrex followed shortly
5 thereafter, in April of 1999, by the advisory committee for
6 the approval of Vioxx and then today and tomorrow, again,
7 the long-term safety studies with these compounds.

8 [Slide.]

9 As mentioned, and what I will do is use the
10 previous slide as kind of the focus for the rest of the
11 talk, the GI paragraph, as it exists, points out to us that
12 there are serious GI toxicities associated with these
13 compounds and they can occur both with and without warning
14 to the patients.

15 Only one in five, or about 20 percent, who develop
16 these serious upper GI events, have any kind of warning
17 symptoms. The GI paragraph notes that patients at risk
18 include those who have a history of prior ulcer or a bleed,
19 are older, are on certain medications or who are in poor
20 health.

21 It notes that these trends basically continue and
22 that the best way to minimize the risk is to use the lowest
23 dose for the shortest period of time.

24 [Slide.]

25 The events that are referred to are often referred

1 to as clinically relevant events in terms of the upper GI
2 tract and, as stated, again in the GI template and the GI
3 paragraph, it has been demonstrated that upper GI ulcers,
4 gross bleeding or perforation caused by NSAIDs appear in
5 approximately 1 percent of patients treated for three to six
6 months and in about 2 to 4 percent of the patients treated
7 for one year.

8 In fact, estimates from the ARAMIS database note
9 that NSAID-induced gastropathy may result in 107,000
10 hospitalizations and 16,500 deaths on an annual basis.

11 [Slide.]

12 So NSAIDs have a certain safety toxicity profile
13 which we have become familiar with. As I have indicated,
14 they are both dose and duration dependent and they involve a
15 variety of organ systems and are reported to us as adverse
16 events, either mild, moderate or severe, as serious adverse
17 events or as deaths.

18 [Slide.]

19 The NSAID template, then, is a more general
20 structure for how we write these labels for NSAIDs. It
21 describes, among other things, precautions, warnings and
22 adverse reactions involving, as we just discussed, the GI
23 tract, but also the liver, the kidney. It describes
24 anaphylactoid reactions, immunologic effects, effects on
25 skin and others.

1 [Slide.]

2 The template, in terms of the liver, notes the
3 metabolic effects of hepatic insufficiency. It notes
4 elevations of the enzymes and sometimes, in 1 percent of the
5 cases, it notes that these can occur up to three times the
6 upper limit of normal. It also points out that there are
7 rare cases of severe reactions involving jaundice, fulminant
8 hepatitis, liver necrosis and hepatic failure and, in fact,
9 some of these can be fatal.

10 [Slide.]

11 It notes, in terms of the kidney, that there are
12 certain pharmacodynamic effects of renal failure or
13 dehydration, that these compounds can have effects on blood
14 pressure, particularly with regards to hypertension, that
15 these compounds, NSAIDs, can cause fluid retention and edema
16 in some settings and can be associated, again, with severe
17 reactions such as renal papillary necrosis, interstitial
18 nephritis and renal failure.

19 [Slide.]

20 In terms of skin, the template notes that there
21 are reactions such as photosensitivity, urticaria and severe
22 reactions including Stevens-Johnson syndrome, toxic
23 epidermic necrolysis and erythema multiforme which, again,
24 can be fatal.

25 [Slide.]

1 For the safety risks, what are the benefits. The
2 efficacy of NSAIDs can be summarized as follows. For OA,
3 they have been indicated for the treatment of
4 osteoarthritis. This is for the signs and symptoms, not for
5 structure or disability as it currently exists in the draft
6 OA guidance document.

7 NSAIDs are also indicated for the treatment of
8 rheumatoid arthritis, again for the signs and symptoms not
9 for structure or improvement in function or remission claims
10 as exist in the current RA guidance document. They are
11 indicated for acute pain and dysmenorrhea as well as other
12 indications such as ankylosing spondylitis, gout, among
13 others.

14 [Slide.]

15 As indicated, there has always been a lot of hope
16 surrounding the Cox-2 field. In fact, in the Wall Street
17 Journal, in '96--this has been shown before at a prior
18 meeting--it was thought that these compounds could not only
19 ease pain but actually slow the disease's debilitating
20 progression. So there has always been a lot of excitement.

21 As indicated, we had a meeting before approval of
22 any of these compounds back in March of 1998. Primarily, it
23 was to discuss the safety issues and what we were hoping
24 would be the approved safety profile of these types of
25 compounds. And then, as now, we presented to our committee

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1 certain questions.

2 For example, we asked them to comment about the
3 degree to which endoscopic studies can distinguish between
4 the currently available NSAIDs and the degree of correlation
5 with clinical outcomes. Some of the comments at that time
6 were that endoscopic studies were generally underpowered to
7 answer these questions we had posed, that the measurable--in
8 this case the endoscopic--might drive out the important--in
9 this case, the clinical outcomes.

10 There was a discussion about the role of endoscopy
11 as a surrogate--how it might turn out to be for the long-
12 term outcomes of interest.

13 [Slide.]

14 We, at that meeting, discussed, then, in terms of
15 the GI warning, what kind of changes might be effected with
16 the Cox-2 agents. We discussed, for example, would removal
17 require the concept of equivalence to placebo, which would
18 have to be mutually defined and agreed to, or, if we could
19 be discussing a major revision, what would that include; for
20 example, substantial reproducible evidence of superiority
21 over NSAIDs and that would include, undoubtedly, endoscopic
22 and clinical endpoints.

23 The discussion was how many NSAIDs would it take.
24 Would it take three? And we would have to obviously agree
25 on which NSAIDs we decided to study.

1 [Slide.]

2 At that meeting, we also discussed the importance
3 of words--for example, the idea of being equivalent to
4 placebo. We had a rather lengthy discussion about saying
5 that two treatments are similar does not necessarily mean
6 that they are the same. From a statistical standpoint,
7 failing to show a difference is not showing equivalence. In
8 fact, equivalence requires that the hypothesis, treatment X
9 and Y are different, be rejected in a trial designed
10 specifically for that purpose. And we talked about that.

11 [Slide.]

12 We also talked about whether we could best view
13 the potential safety advantage of Cox-2 agents on a
14 mechanistically based origin. For example, on one extreme
15 where Cox-2 was felt not to be present in the platelets, we
16 would have one result. On the other hand, where Cox-2 was
17 present, such as in kidney, we would have yet an opposite
18 result.

19 It was clear to us that this field was evolving
20 rapidly and targets were appearing where they initially
21 hadn't been found. So we might then be in a position where
22 Cox-2 may be present in some situations and it may not be
23 present in other situations. The stomach may be an example
24 of that and we might, then, get an intermediate result.

25 [Slide.]

1 If then, again at this meeting, discussing if the
2 Cox-2 agents were different, were they, in fact,
3 representatives of a different class. And we discussed how
4 many agents it would take to define that class. We were
5 curious, in terms of how more potent inhibitors, if they
6 were to be developed, how they might fit into this scheme.

7 We, again, discussed the label, whether we would
8 revise the current NSAIDs template or, in fact, write an
9 entirely new label, depending on the data. There was always
10 the question of, in these trials, whenever we were
11 discussing results, how many of the results were actually
12 testing the drug, the theory of how the drug should be
13 working, or a combination of both.

14 [Slide.]

15 We always had an eye to the future, wondering
16 about other indications. For example, as I alluded to
17 earlier, any kind of structural modification, OA or RA. We
18 had been hearing about prophylaxis for colon cancer and we
19 had also been hearing about prophylaxis of Alzheimer's
20 disease.

21 We were certainly aware, and would not have been
22 surprised, if we would have seen some unique adverse events
23 associated with these particular compounds. Of course, we
24 were very interested in the safety and efficacy in children
25 because NSAIDs had typically not been studied in an

1 organized fashion.

2 [Slide.]

3 In December, then, at the end of 1998, celecoxib,
4 or Celebrex, was submitted and discussed. It was, as I have
5 indicated at the bottom there, a large submission, lots of
6 information. From that information, we were able to glean
7 the following.

8 [Slide.]

9 In terms of OA, Celebrex was found to be at doses
10 from 100 to 200 milligrams BID more effective than placebo.
11 However, it did not appear that there was any obvious
12 efficacy advantage of the 200 milligram BID dosing and it
13 appeared that 100 milligrams BID was about the same as 200
14 milligrams on a daily basis.

15 The efficacy, in terms of the treatment for OA,
16 was comparable to naproxen at 500 milligrams BID and we
17 noted, in the long-term safety trials that were part of the
18 NDA, that most patients, in this case, about 70 percent,
19 increased their dose in the open-label experience and this
20 has been known in the literature as the dose creep.

21 [Slide.]

22 In the NDA, then, for Celebrex, it was also
23 indicated for treatment of RA, at doses from 100 to
24 400 milligrams BID, found to be more effective than placebo.
25 There was no obvious, again, efficacy advantage of going up

1 to the higher dose of 400 milligrams BID, though. Once
2 more, comparable to naproxen at 500 milligrams BID and,
3 again, we noted that, in the open-label experience, about
4 70 percent of patients increased their dose, again an
5 example of the dose-creeping phenomenon.

6 [Slide.]

7 The NDA did not allow us to give the indication
8 for treatment of acute pain and dysmenorrhea.

9 [Slide.]

10 So we discussed, at that time, the Cox-2
11 hypothesis and wondered how Celecoxib would fare against
12 that. It was really a representative of that, particularly
13 as we discussed efficacy because, as indicated, the
14 analgesic efficacy appeared to be less than NSAIDs for acute
15 pain. So we wondered if the problem was really with the
16 models that were selected in the particular NDA.

17 We wondered if it was due to the nature of acute
18 versus chronic pain and did this have something to do with
19 the induction of Cox-2, or we wondered whether this was
20 related to the potency or selectivity of celecoxib, among
21 other reasons.

22 We also discussed that, in these studies, there
23 didn't any obvious efficacy advantage compared to NSAIDs for
24 OA and RA, but we wondered what would happen in long-term
25 trials.

1 [Slide.]

2 Then, as indicated later on, the NDA for Vioxx was
3 submitted and, in there, was sufficient information for
4 labeling for OA and it was found that, at doses of 12.5 and
5 25 milligrams on a daily basis were better than placebo.

6 Once more, there didn't appear to be any obvious
7 efficacy advantage of the higher dose at 25 milligrams
8 daily. The efficacy was found to be comparable to ibuprofen
9 at 800 milligrams TID and diclofenac 50 milligrams TID and
10 there was no information for us to get any idea of what
11 would happen in an open-label experience.

12 [Slide.]

13 For RA, there was no data submitted in the NDA.

14 [Slide.]

15 For pain, Vioxx was indicated for acute pain and
16 dysmenorrhea at doses of 50 milligrams daily and, in five-
17 day studies, was found to be more effective than placebo.

18 [Slide.]

19 So, at this point in time, it appears that, in
20 terms of efficacy for COX-2 agents like NSAIDs, they are
21 indicated for the treatment of signs and symptoms of
22 osteoarthritis. This is both, again, for Celebrex and
23 Vioxx. They are indicated for the treatment of rheumatoid
24 arthritis, and this is only for Celebrex, at what is now
25 called the 'x' dose.

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1 They are indicated for the treatment of acute pain
2 and dysmenorrhea. This is only for Vioxx. They are
3 indicated also for the treatment of a rare form of cancer
4 known as familial adenomatous polyposis, or FAP. This is
5 only for Celebrex and this is now at what we call the 2X
6 dose as adjunctive therapy in this particular condition.

7 [Slide.]

8 So, despite their long history of usage, no NSAID
9 has been tested in a large and simple long-term safety trial
10 at doses exceeding the upper limit of the approved labeling
11 in arthritis, particularly at the 2X dose. So we are really
12 going into uncharted waters here. Again, we are always
13 looking to the future.

14 Thank you.

15 DR. HARRIS: Thank you very much, Dr. Witter. We
16 will have a discussion this afternoon. We are going to
17 limit any questions the committee might have to just
18 clarification, or whether or not there is any clarification
19 required with respect to Dr. Witter's presentation.

20 Seeing none, we will move to the next item on the
21 agenda and that will be the presentation by G.D. Searle and
22 Company. Dr. Philip Needleman will introduce.

23 **G.D. Searle and Company Presentation**

24 **Introduction**

25 DR. NEEDLEMAN: Thank you very much. Good

1 morning.

2 [Slide.]

3 We have been asked by the agency to continue to
4 extend the tutorial points about some aspects of the history
5 and discovery of COX-2 inhibitors and set a context for
6 today's review.

7 [Slide.]

8 This will be the agenda that we will proceed
9 under. I will start with the introductory remarks. I am
10 the chief scientist of Pharmacia and the Chairman of
11 Research and Development.

12 [Slide.]

13 In 1990, based on our discoveries, we discovered
14 the existence of a novel isoform of cyclooxygenase, the
15 enzyme that produces prostaglandin. We discovered that the
16 newly produced enzyme was intimately associated with
17 inflammation and pain and swelling.

18 So we set forth this hypothesis that said that
19 there were two enzymes. One was a housekeeping enzyme, a
20 constituent of one, which maintained a physiological
21 function, and those functions were especially prominent in
22 gastrointestinal tissue where the prostaglandin was involved
23 in the synthesis of mucus which protects the stomach and
24 intestine from acid and enzymes. It was also especially
25 present as an enzyme in platelets, and that was COX-1.

1 We further hypothesized that all existing NSAIDs,
2 aspirin-like drugs, were nonselective and inhibited both
3 enzymes, and indeed these are potent agents and their
4 mechanism of action was the treatment of prostaglandins
5 produced at the site of inflammation.

6 Their problem and limitation was they also
7 produced mechanism-based side effects by blocking
8 prostaglandins especially in the gastrointestinal tract and
9 in platelets.

10 This hypothesis was the primary drive of our
11 enormous effort to seek out, and what eventually led to, the
12 discovery of celecoxib Celebrex to achieve the efficacy of
13 NSAIDs, but with a far superior GI profile.

14 [Slide.]

15 Now, in the 1998 NDA, we established that here a
16 dose response curve in rheumatoid arthritis patients was
17 fully equivalent in efficacy to the widely used naproxen
18 without evidence of endoscopic damage here being similar
19 through 400 mg BID to placebo, but statistically well less
20 than the 25 percent incidence of endoscopic ulcers induced
21 with naproxen and all the other NSAIDs.

22 [Slide.]

23 So, for a perspective, as you just heard, it was
24 reviewed in December of '98 and approved by the end of
25 December 1998, and it was based on its demonstrated

1 endoscopic upper GI safety compared to conventional NSAIDs
2 For the context which you just heard, endoscopy
3 was regarded as a surrogate, so indeed the warning labels
4 for Celebrex reflected that NSAID template. So, this large,
5 well-designed trial was designed to achieve really greatly
6 expanded and clinically meaningful GI safety with the design
7 intended to go for differentiation of that warning label
8 based on the superior safety of Celebrex versus NSAID.

9 [Slide.]

10 Now, the class trial's primary objective was the
11 GI safety, but inherently we will be able to comment on the
12 systems you saw reviewed - the renal, the cardiovascular,
13 and so on.

14 This proved to be a quite complicated and rigorous
15 trial. We chose and worked actively at all stages of this
16 to frequently interact and collaborate with the agency, and
17 we designed a trial that really followed the practice of
18 medicine, so we enrolled both OA patients and RA patients,
19 we used multiple NSAIDs, and we allowed cardiovascular use
20 of low-dose aspirin because this age population in practice
21 was using these for cardioprotection.

22 We used two NSAIDs, agreeing with the agency that
23 we should include ibuprofen because it was regarded as a
24 safer NSAID, and so we wanted two NSAIDs and really to
25 compare to the one that had the higher safety.

1 Furthermore, as you heard, kind of in an
2 unprecedented way, we used a dose that was 2X the maximum
3 dose in rheumatoid arthritis and was actually 4 times the
4 dose, the maximally achieved dose used for Celebrex in
5 arthritis, but we compared that with the commonly used
6 doses, not even the maximum doses, of the ibuprofen and the
7 diclofenac. So, it was an exaggerated trial to really see
8 the scope of the GI safety and have a long term sense of
9 their utility and their improved potential.

10 [Slide.]

11 So, in the context that we were asked by the
12 agency to then say, okay, what do you know in 2001 about the
13 COX-2 hypothesis that you didn't know in 1990 and really
14 started the large program.

15 Well, the bulk of the information is fundamentally
16 the same. Indeed, there are two enzymes. It is clear in
17 COX-1 that it is restricted to the stomach, the intestine.
18 In the kidney it maintains renal blood flow. The platelets
19 are only COX-1, and platelets are cells that don't have a
20 nucleus, so if you use an aspirin-like drug, you will
21 irreversibly block that COX-1. NSAIDs, all NSAIDs hit COX-
22 1, as well as COX-2, but those are transient inhibition.

23 It also became clear, and we were asked to talk
24 about this role of COX's in platelets and endothelium. The
25 endothelial cells and the blood vessels, smooth muscle cells

1 are all normally constituents of COX-1. Their product is
2 PGI2.

3 Now, on the COX-2 side, indeed, inflammation of
4 all sorts is associated with COX-2 expression, and it is an
5 enzyme that is induced and it is not normally there. We now
6 know that nearly every epithelial tumor expressed COX-2, in
7 precancerous steps, at cancerous, and in metastatic stages,
8 and as Jim Witter showed you, we achieved approval of the
9 pretreatment of a regression of precancerous polyps, the
10 familial adenoma polyposis, and large trials are underway in
11 colon cancer and other cancers.

12 It is now clear in the next three that COX-2 also
13 exists in the physiological maintenance especially in some
14 species of kidney function. It is present constitutively
15 in the central nervous system, and it plays a large role in
16 female reproduction.

17 Finally, endothelium has inducible enzymes and in
18 certain kinds of treatments, there can be some induction of
19 COX-2. So, then this is the setting for the CLASS trial
20 where you have that large database to look back to see did
21 you unmask unique side effects.

22 [Slide.]

23 The CLASS trial then definitely will allow us to
24 shed light on the roles of COX-1 and COX-2 on the GI events
25 and actually on the blood loss which we think also reflects

1 GI events.

2 We have data to really possibly comment about the
3 implications of low dose aspirin, because in the end now we
4 have a large prospective trial with a large database about
5 low dose aspirin, and could at least comment about the
6 possible issues about cardiovascular, renal, and thrombotic
7 events.

8 What this trial won't add to is this is largely an
9 aged population, so there won't be evidence about female
10 reproduction. A CNS trial has completely different
11 parameters and endpoints, and wasn't doable, and again, the
12 cancer trials are completely different trials, and the long
13 term trials are three years in treatment. So, we can
14 comment in these two areas.

15 [Slide.]

16 We were asked to talk about--and it is an
17 important point--about then the use of low dose aspirin, so
18 we are talking about 325 milligrams or less. Aspirin,
19 because it is capable of acetylating a serine in the active
20 side of cyclooxygenase, irreversibly inhibits that enzyme
21 and platelets lacking the nucleus can never reconstitute new
22 enzyme, so one dose of aspirin permanently wipes out
23 platelets. That is by blocking the cyclooxygenase which
24 makes thromboxin, which is the aggregator constrictor
25 substance. Similarly, that is the mechanism basis of the

1 increase in bleeding potential.

2 So, in '98 when this was approved, I think there
3 were 18 or 20 NSAIDs proved to be nonspecific, very potent
4 on COX-2, very potent on COX-1. All NSAIDs transiently
5 inhibit platelet COX-1 and the thromboxane production, and
6 there is no difference if it's ibuprofen, diclofenac, or
7 naproxen.

8 Now, aspirin also has the property of being a
9 direct irritant and damaging the GI mucosa. Importantly, in
10 a recent New England Journal of Medicine paper--and there is
11 a number of important papers--low dose aspirin, this 325
12 milligrams or less, shows the increased risk of GI ulcer
13 complications on its own.

14 So, with this context, we could take a look and
15 see what the CLASS data says about the GI side effects of
16 aspirin.

17 [Slide.]

18 Now, in the renal system, it is clear now because
19 you have the cDNA probes and the antibodies that both
20 isoforms are expressed constitutively, that is, it is
21 normally there and is turned on inactive.

22 The confusion starts to occur when you look at the
23 anatomical distribution of the enzyme. The most studies
24 were in rat especially and in dog where there was high
25 expression in the kidney at the sites of renin production,

1 and indeed you can see COX-2 effects. On the other hand,
2 primates and humans don't have expression in the same site,
3 so that is not so clear.

4 The database did not distinguish between Celebrex
5 and NSAIDs, so in terms of increased edema, both Celebrex
6 and NSAID had a response, but Celebrex did not exhibit a
7 dose-dependent increase in that response.

8 [Slide.]

9 Importantly, we were asked about the
10 cardiovascular and thrombosis. As you know, low dose
11 aspirin is especially used in the treatment, in the
12 secondary prevention of myocardial infarction, and this
13 mechanism-based response is due to the irreversible
14 inhibition of the platelet COX-1 to block thromboxin.

15 So, there is clear and substantial evidence that
16 low dose aspirin is a benefit during an acute myocardial
17 infarction, during unstable angina, and clearly a benefit in
18 the secondary prevention of myocardial infarction.

19 In terms of primary prevention, it is a marginal
20 case and there is no clear demonstration anywhere near as
21 clear as the secondary prevention.

22 Now, in that context, we will remind you that
23 blood vessel smooth muscle and endothelium produces
24 prostacycline PGI₂ predominantly from COX-1. That is the
25 opposite of thromboxane in the platelet which causes

1 aggregation. PGI2 is anti-aggregatory and vasodilate.

2 Now, it is normally only COX-1, but part of the
3 issue with that could be turned on there, so you are
4 thinking about the site of interaction in blood vessels of
5 platelet and endothelium.

6 What you have to remember, though, is the
7 endothelium makes continuously prodigious amounts of nitric
8 oxide which in its own right is a very potent antithrombotic
9 and is a potent vasodilator, and nitric oxide sensates in
10 blood vessel is not inhibited by NSAIDs or COX-2. So, the
11 aspirin story or NSAID story doesn't affect the endothelial
12 nitric oxide.

13 [Slide.]

14 Now, to illustrate the doses in patients that were
15 COX-2 selective, from the NDA I could show you data on
16 platelet aggregation, so this is platelets removed from
17 patients and treated with arachidonic or other stimuli to
18 measure aggregation.

19 You see placebo in the white bar. Here, we went
20 to 600 mg twice a day, well above even the exaggerated dose
21 we used in this CLASS study, and you see no inhibition of
22 platelet aggregation. Here, you see inhibition by
23 diclofenac, and you can show full-range dose response curves
24 through the 1,200 mg, and it is COX-2 selective dose without
25 inhibition of COX-1.

1 [Slide.]

2 Now, that is pertinent and the reason this is a
3 question at all is this data was published by McAdams, it is
4 from the Garrett Fitzgerald data in which they looked at
5 human urinary PGI2 metabolites, PGIM, and looked at placebo,
6 does of Celebrex that were COX-2 selective and didn't affect
7 COX-1, and looked at doses of ibuprofen.

8 What you see is a suppression of these PGI
9 metabolites. Since that was a dose that was COX-2
10 selective, that suggested that there was some COX-2
11 generated PGI2. Now, we don't know if that is from the
12 epithelium because it is urine, but then this is the basis
13 of the hypothetical consideration.

14 [Slide.]

15 So, the question is, is that PGI2 inhibiting
16 platelet aggregation, and this work suggests if it was
17 endothelial, which we couldn't tell, that you would be
18 affecting that PGI2 and endothelium.

19 [Slide.]

20 So, here is a cartoon of their hypothesis. If
21 thrombosis is on this balance beam, it is the platelet COX-1
22 that is causing aggregation, and it could theoretically be
23 the prostacycline, PGI2, made in the endothelial cell.

24 Since NSAIDs would block both, the beam would stay
25 balanced and there would be no effect on thrombosis,

1 however, if COX-2 inhibitors were around, you would suppress
2 this, thromboxane could be dominant, and you would have the
3 potential for the risk of a thrombotic event.

4 So, if the hypothesis is correct--and remember by
5 and large endothelial cells still are predominantly COX-1,
6 if it is correct, then, the expected effect of COX-2
7 inhibitors would be similar to patients not taking the low
8 dose aspirin in an at-risk population.

9 [Slide.]

10 So, what about the CLASS data? What can we say
11 about the potential for assessing the risk? The
12 cardiovascular benefit of aspirin--and now here we are even
13 talking about the secondary prevention because there is no
14 case for primary prevention--the question was the ability of
15 aspirin to reduce the primary event or, similarly, what is
16 the ability of a COX-2 inhibitor to cause a cardiovascular
17 event.

18 If you look at something like Physicians Health
19 Study, the sample size required would be greater than 20,000
20 patients for five years to find the event. So, therefore,
21 the CLASS trial, we had 8,000 patients, but only 4,000
22 patients on Celebrex, was never large enough to detect such
23 a small cardiovascular event due to COX-2 inhibition of
24 endothelial cells.

25 In other words, with this sample size, you can't

1 show a mechanism-based event, a cardiovascular event.
2 However, the CLASS trial was large enough for general
3 cardiovascular safety and renal safety, or in other words,
4 if you would see a thrombotic event with this small of a
5 trial, it can't be mechanism based, it would have to be
6 molecule based because the trial is inadequate in size.

7 [Slide.]

8 So, in summary, and what we will review with you
9 today, is we feel that there a preponderance of clinical
10 data which exhibits the safety of COX-2 inhibition and
11 Celebrex compared to NSAIDs which would warrant the change
12 of the NSAID platelet.

13 That is built on now this continuum of data,
14 started with the endoscopy of nearly 5,000 patients in the
15 NDA, it's this 8,000 patient trial with evaluation of ulcers
16 and complications in the CLASS trial, and it's this very
17 large postmarketing surveillance.

18 We looked at the exaggerated doses, the 2 to 4X of
19 the RA and OA dose, and in that trial, as you heard asked
20 before, there was no new safety signal even in this long-
21 term trial with the exaggerated dose, and we think that
22 Celebrex did not increase the thromboembolic events compared
23 to NSAID, and that was true both in the absence and the
24 presence of aspirin.

25 [Slide.]

1 So, with this as a setting, we will lay out the
2 context of the clinical trial and the data, and we will
3 start with Dr. Steven Geis.

4 **UGI Safety Profile of NSAIDs and Celecoxib:**

5 **Rationale for CLASS Study**

6 DR. GEIS: Good morning.

7 [Slide.]

8 In my presentation, I will review the history of
9 our understanding of NSAID-associated upper GI toxicity and
10 review the prospective trials that were used to evaluate the
11 upper GI toxicity of NSAIDs, and then finally discuss the
12 upper GI safety data on celecoxib that we had at the time of
13 the submission of the NDA.

14 [Slide.]

15 In reviewing the NSAID-associated upper GI
16 toxicity, I first want to review the various types of
17 toxicity that have been appreciate over the years, incidence
18 of this type of damage, and then to define who are the
19 patients at risk.

20 [Slide.]

21 Now, in the 1970s and 1980s when NSAIDs became
22 widely used to treat the approximately 44 million arthritis
23 patients in the U.S., physicians began to be aware that
24 patients were, in fact, developing side effects associated
25 with NSAIDs, and these were predominantly upper GI in

1 nature.

2 These included symptoms, but the symptoms also
3 evolved into symptomatic ulcers. These ulcers, in turn,
4 could become complications, that is, the ulcers could bleed,
5 they could perforate, or, in fact, form outlet obstruction
6 in the stomach.

7 [Slide.]

8 Now, this slide shows the type of endoscopic
9 appearance of an ulcer that a patient might have had during
10 that time. That is, the patient would have a symptom, the
11 clinician would perform an endoscopy and observe this type
12 of an ulcer which, in that terminology, is called a
13 symptomatic ulcer.

14 [Slide.]

15 In some cases, the ulcer was proximal to a blood
16 vessel and if the lesion progressed, the blood vessel could
17 be eroded and we would have a bleeding ulcer or an ulcer
18 complication.

19 [Slide.]

20 Also, the ulcers could erode completely through
21 the wall of the stomach or the intestine forming a
22 perforation, and as everyone can see from this type of
23 typical x-ray from a patient who has had a perforation, we
24 have free air under the diaphragm.

25 [Slide.]

1 So, as time progressed, clinicians became aware
2 that there was a spectrum of NSAID-related upper GI injury
3 which ranged from symptomatic ulcers and easily could form
4 an ulcer complication, the bleed or the perforation.

5 [Slide.]

6 Now as our understanding progressed, certain
7 acronyms and definitions began to evolve and develop and are
8 seen in the literature. Over time, symptomatic ulcers,
9 perforations, and bleeds became referred to as PUBs,
10 whereas, perforations, outlet obstructions, and bleeds
11 became referred to as POBs.

12 In my presentation and those of my colleagues
13 today, we won't be using this terminology, we will be
14 referring to NSAID toxicity as symptomatic ulcers or ulcer
15 complications.

16 [Slide.]

17 To determine an understanding or to establish an
18 understanding of the magnitude of the problem, over the
19 years observational cohort and retrospective cohort or case
20 controlled studies were performed, and in these studies, the
21 investigators examined hospital records for diagnoses of
22 patients who had symptomatic ulcers or ulcer complications,
23 and then looked to see if there was an association with
24 NSAID use. In this manner, they were able to establish what
25 is really the rate of these types of toxicities with NSAIDs.

1 [Slide.]

2 They found--and this was repeated by several
3 investigations, and as Dr. Witter pointed out--that it was
4 established that the overall incidence of the symptomatic
5 ulcers and the ulcer complications was on the order of 2 to
6 4 percent per year. These retrospective analyses also gave
7 us evidence that some of the ulcer complications were
8 symptomatic, but also some of them were not symptomatic,
9 that is, there was no heralding symptom prior to the actual
10 bleeding or the perforation taking place.

11 It really depends upon what study you read what is
12 the percentage of these types of toxicities that are
13 actually asymptomatic complications, and it can range
14 anywhere as low as 10 percent up to 60 percent depending
15 upon the study.

16 The retrospective studies also allowed us to look
17 at what is the background rate of this type of toxicity in
18 patients not using NSAIDs.

19 [Slide.]

20 As we see here from the work of Dr. Singh and Dr.
21 Perez-Gutthan, that in NSAID users indeed the incidence of
22 ulcer complications by their studies was on the order of
23 about 1.3 to 1.7 percent per year, but in non-NSAID users
24 the rate was about 6-fold lower, on the order of about .03
25 percent per year, so we knew there was a background rate,

1 and in NSAID users, these very serious complications
2 occurred about 7 times more frequently.

3 [Slide.]

4 Also, investigators were able to estimate what was
5 the mortality due to the GI toxicity of NSAIDs, and here we
6 show the Aramis database, as well as the Tennessee Medicaid
7 database. The Aramis database predicted that the number of
8 deaths in the U.S. due to NSAID GI toxicity was about 1.3
9 per 1,000 patient years, and then estimating that based on
10 13 million patient years of exposure in the U.S., this would
11 equate to approximately 16,500 deaths per year in the U.S.
12 alone due to NSAID GI toxicity.

13 In the Tennessee Medicaid database, they estimated
14 that in the elderly, defined as 65 years of age or older,
15 that the rate of death due to NSAID GI toxicity was about
16 1.4 per 1,000 patient years. Estimating the patient years
17 of exposure in the elderly of about 2 million, they
18 estimated that there is about 3,300 deaths in the U.S. in
19 the elderly due to NSAID toxicity.

20 [Slide.]

21 The retrospective studies also gave us an idea of
22 who are the patients at risk of such problems. Although
23 there were many risk factors identified, those which
24 consistently were the most correlated with the complications
25 were increasing age, a history of an ulcer or GI bleeding,

1 the dose of the NSAID, and the duration of the NSAID use, as
2 well as the use of low dose aspirin.

3 [Slide.]

4 This slide shows the work of Perez-Gutthan, which
5 shows the odds ratios for ulcer complications as a function
6 of age. What we see is in females and in males, that with
7 increasing age, in patients not taking NSAIDs, there is an
8 increased rate of developing or an increased risk of
9 developing an ulcer complication. However, in the NSAID
10 users, that rate is about 5 times higher in all age groups.
11 So, although there is a correlation between age and the
12 likelihood of developing a complication, even the young
13 patients are on NSAIDs are at risk of developing a
14 complication.

15 [Slide.]

16 Here, we show the work of Dr. Weil which looked at
17 the risk of upper GI bleeding related to prophylactic
18 aspirin use. The odds ratio ranged from 2 to 4 at doses of
19 75 mg to 300 mg, all of which are considered prophylactic
20 doses of aspirin.

21 [Slide.]

22 The work of Henry looked at the risk of upper GI
23 bleeding of various types of NSAIDs. In this work, they
24 used ibuprofen as the reference NSAID, so if you will, they
25 considered ibuprofen to be the safest although we know that,

1 in fact, is not the case.

2 Nevertheless, using that as the reference, they
3 found that the risk of upper GI bleeding with all the NSAIDs
4 was high and was certainly statistically higher than that
5 seen with ibuprofen based on this study.

6 [Slide.]

7 So, in conclusion, based on the retrospective
8 studies that were conducted and the observations made by
9 investigators, it was found that symptomatic ulcers and
10 ulcer complications really are on a continuum of GI
11 toxicity, all NSAIDs are associated with this type of
12 toxicity, and approximately 16,500 deaths occur per year in
13 the U.S. due to NSAID toxicity.

14 [Slide.]

15 Now, I would like to look at the prospective
16 trials that evaluated NSAID upper GI safety, looking at the
17 endpoints of endoscopic ulcers and the one study that used
18 ulcer complications as an endpoint.

19 [Slide.]

20 Now, if we can refer back to the definitions once
21 more, so we now have symptomatic ulcers and endoscopic
22 ulcers. Symptomatic ulcers are a form of upper GI toxicity
23 encountered in clinical practice, and these are identified
24 by a "for cause" endoscopy.

25 On the other hand, endoscopic ulcers are measures

1 of GI toxicity in clinical investigations, and these are
2 identified by a scheduled endoscopy in the course of a
3 clinical trial.

4 [Slide.]

5 The endoscopic ulcer studies really confirmed what
6 we observed in our retrospective assessments, so here we
7 show the prevalence of endoscopic upper GI ulcers for
8 various NSAIDs, and what is seen is that all NSAIDs were
9 associated with upper GI ulceration at a rate of about 20 to
10 30 percent.

11 This work was confirmed by a variety of
12 investigators who did similar types of endoscopic studies
13 and found that NSAIDs produce a point prevalence of ulcers
14 in the stomach and the duodenum ranging anywhere from 5
15 percent up to as high as about 30 percent.

16 [Slide.]

17 The endoscopic studies also confirm the
18 relationship of GI toxicity with NSAIDs and age. Here, we
19 show the work of Cheatum showing that the point prevalence
20 of ulcers as a function of age increases, but importantly,
21 even the younger patients in the range of 30 to 39 years old
22 did have a high incidence or a high point prevalence of
23 NSAIDs ulceration.

24 [Slide.]

25 As Dr. Witter pointed out, the question became:

1 Are endoscopic ulcers really surrogates of ulcer
2 complications?

3 [Slide.]

4 Actually, it seemed to make sense. NSAIDs reduce
5 mucosa prostaglandins, and we know thereby causing ulcers.
6 Ulcers can result due to erosion through a vessel or erosion
7 through the wall of the stomach of the duodenum, and
8 bleeding perforation or outlet obstruction, but we couldn't
9 be sure that the endoscopic ulcers really did predict this.

10 Where we really found that to be true was in the
11 development program for misoprostol, which is a synthetic
12 prostaglandin, and based on this program, we were able to
13 show a relationship between endoscopic ulcer data and ulcer
14 complications.

15 [Slide.]

16 I would first like to show you the results of an
17 endoscopy trial using misoprostol. This was a one-year
18 study in patients with osteoarthritis or rheumatoid
19 arthritis.

20 All patients were endoscoped at baseline and then
21 endoscoped at various points during the trial. Half the
22 patients received an NSAID plus placebo, whereas, the other
23 patients received the NSAID plus the synthetic
24 prostaglandin.

25 [Slide.]

1 This slide shows the results of that study. Over
2 a one-year period, the incidence of ulcers in patients who
3 received the NSAID plus placebo was about 30 percent. The
4 patients who received the NSAID plus the synthetic
5 prostaglandin was reduced in half to 15 percent, so a 50
6 percent reduction.

7 [Slide.]

8 We then conducted the MUCOSA trial, and this was
9 to look at the effects of the synthetic prostaglandin on
10 clinically relevant outcomes. It was a prospective,
11 randomized, double-blind trial where the primary endpoint
12 now was ulcer complications defined as bleeding,
13 perforation, and obstruction.

14 [Slide.]

15 It was designed to parallel normal medical
16 practice in that scheduled endoscopies were not performed,
17 they were only performed for cause.

18 [Slide.]

19 This slide shows that we prospectively formed a GI
20 Events Committee that provided definitions of what an ulcer
21 complication would be in the MUCOSA trial, and these
22 definitions really became the basis of definitions we use in
23 the celecoxib program.

24 [Slide.]

25 Here, we show the results of the MUCOSA trial.

1 Over time, the incidence of ulcer complications in the
2 NSAID-treated group increased, and those who received
3 misoprostol plus the NSAID, the rate was reduced by
4 approximately 50 percent.

5 [Slide.]

6 So, these prospective studies taught us that
7 endoscopic ulcers and ulcer complications really are
8 reliable endpoints for investigating GI safety, and
9 endoscopic ulcers are indeed predictive of ulcer
10 complications. The most important information that confirms
11 this is that exogenous prostaglandins reduce both endoscopic
12 ulcers and ulcer complications by approximately 50 percent.

13 [Slide.]

14 Now, I would like to follow up on what we knew
15 about the upper GI safety of celecoxib in the NDA in 1998
16 using endoscopic ulcers, as well as ulcer complications as
17 endpoints.

18 [Slide.]

19 At that time, we had performed endoscopies in over
20 4,700 arthritis patients. The results of the trials showed
21 us that the incidence of upper GI ulcers was similar to
22 placebo, and this was replicated, and statistically lower
23 compared to traditional NSAIDs, such as naproxen,
24 diclofenac, and ibuprofen.

25 [Slide.]

1 This slide shows the results of two of the
2 studies, one of which Dr. Needleman previously described.
3 There were three-month endoscopy trials. One was in OA
4 patients, one was in RA patients, and each involved over
5 1,000 patients.

6 We compared the incidence of ulcers in placebo to
7 celecoxib and then the NSAID naproxen. Celecoxib was
8 similar to placebo at all doses even at the high dose of 400
9 mg twice a day, which is much higher than the approved
10 therapeutic doses for OA and RA, and was statistically lower
11 than that seen with naproxen.

12 [Slide.]

13 This slide shows one of the studies that was
14 submitted at that time, which was a six-month endoscopy
15 trial, comparing celecoxib to diclofenac. Once again, we
16 showed a lower incidence of upper GI ulcers with celecoxib
17 compared to diclofenac.

18 [Slide.]

19 In the program for celecoxib, we also looked at
20 analysis of upper GI ulcer complications. Let me describe
21 the methodology for collecting that data briefly.

22 We formed an external GI Events Committee that
23 established criteria or definitions for upper GI
24 complications, and this was defined prospectively.

25 The data then came from 14 randomized controlled

1 trials and one open-label trial, all of whom involved OA and
2 RA patients. Patients who the investigators thought might
3 be having an ulcer complication were then submitted to the
4 GI Events Committee, who based on their definitions
5 determined whether or not a complication really had or had
6 not occurred.

7 In this whole process, the GI Events Committee was
8 blinded to the trial and blinded to the study drug that the
9 patient was on.

10 [Slide.]

11 The definitions of ulcer complications were
12 similar to MUCOSA and are shown here.

13 [Slide.]

14 Also, these controlled trials were actually very
15 extensive. They involved over 11,000 patient. The open-
16 label trial involved over 5,000 patients. The controlled
17 trials were 12 weeks in duration, the open-label two years,
18 and the doses of celecoxib ranged from 200 to 400 mg per
19 day.

20 [Slide.]

21 This slide shows the results of this analysis.
22 From the controlled trials, in the NSAID-treated patients,
23 the ulcer rate, the annualized ulcer rate was about 1.7
24 percent, with celecoxib it was only 0.2 percent, again,
25 about a 7-fold reduction and similar to what was seen in

1 placebo and similar to what was seen in the literature for
2 the background rates.

3 In the open-label trial, we also showed an
4 incidence or an annualized incidence of about 0.2 percent.

5 [Slide.]

6 So, our conclusions at that time were that the
7 incidence of endoscopic ulcers with celecoxib were similar
8 to placebo and lower than NSAIDs, that endoscopic ulcer data
9 were, in fact, predictive of the ulcer complication data,
10 and that there was a lower incidence of ulcer complications
11 with celecoxib compared to NSAIDs.

12 [Slide.]

13 However, the generalizability of the ulcer
14 complication data was uncertain at that time because in the
15 14 randomized trials or controlled trials, many of these
16 trial were endoscopy studies in which the patients were
17 proven to be ulcer free by endoscopy at the start of the
18 study.

19 So, about 40 percent of the patients in the
20 analysis were really ulcer free, and the question was, well,
21 is that data generalizable to the entire population, and in
22 addition, most of the studies were three months in duration.

23 [Slide.]

24 So, this became the rationale for conducting the
25 CLASS trial. We wanted to step forward and do a rigorous

1 assessment of the upper GI safety of celecoxib using
2 clinically relevant outcomes in a patient population that
3 fully represents the intended population and also to observe
4 this with chronic exposure of celecoxib.

5 [Slide.]

6 Therefore, in brief, the design was a large
7 prospective study. We wanted it to mirror normal medical
8 practice, that is, endoscopies were performed only for
9 cause. We wanted it to include a broad spectrum of
10 patients, OA and RA patients.

11 We included high risk patients, that is, those who
12 had comorbidities and those who were using low dose aspirin.
13 As Dr. Needleman pointed out, we used the dose of celecoxib
14 which was 400 mg twice a day, 4 times the OA dose and 2
15 times the highest RA dose, and the duration of the trial
16 extensive. Patients were allowed to participate for up to
17 15 months.

18 I would now like to turn the podium to Dr.
19 Lefkowitz, who will review the trial in more detail and the
20 results.

21 **Safety Profile of Celecoxib:**

22 **CLASS, Long Term Safety Trial**

23 DR. LEFKOWITH: Good morning.

24 [Slide.]

25 The celecoxib long-term arthritis safety study, or

1 CLASS for short, was performed to further explore the GI and
2 general safety attributes of celecoxib.

3 [Slide.]

4 Before sharing with you the results of this
5 landmark clinical trial, I would like to review for you the
6 elements of study design. As the speakers before me have
7 indicated, this was intended to be a "real world" study in
8 that clinical practice conditions were reproduced as closely
9 as possible.

10 Accordingly, the full spectrum of arthritis
11 patients were enrolled, patients with OA, as well as RA.
12 Moreover, patients were allowed to use low dose aspirin.
13 Cardiovascular disease is a common comorbidity within the
14 arthritis patient population.

15 Moreover, this was a stringent test of safety in
16 that celecoxib was administered at 2 times to 4 times the RA
17 and OA doses that were shown to be maximally effective, and
18 compared to both ibuprofen and diclofenac, widely used
19 NSAIDs. Again, ibuprofen has been regarded as one of the
20 safest of the conventional NSAIDs.

21 [Slide.]

22 In discussing the design elements of the trial, I
23 would like to review for you briefly the study objectives,
24 the protocol design, the analytic plan, as well as the
25 oversight committees and their function, these oversight

1 committees supervising the trial performance.

2 [Slide.]

3 The objectives of the trial were 3-fold.

4 Celecoxib was to be compared with NSAIDs consisting of
5 ibuprofen and diclofenac with respect to the incidence of
6 ulcer complications and symptomatic ulcers. Moreover, the
7 study intended to examine for risk factors for such
8 outcomes, and for the effect of such risk factors on
9 outcome.

10 Specifically included was an analysis of aspirin
11 as a risk factor. Finally, the study was intended to
12 compare the general safety and tolerability of celecoxib to
13 the NSAID comparators.

14 [Slide.]

15 Turning now to the study design, the CLASS study
16 was double-blind, randomized, parallel group study that was
17 separated into two protocols that were performed
18 contemporaneously, which were identical save for the
19 comparator employed. They were designed to be analyzed in a
20 pooled fashion. All patients were to be allowed an
21 opportunity to participate for at least six months.

22 The inclusion and exclusion criteria were
23 constructed in a way to replicate clinical practice.
24 Accordingly, patients who had a clinical diagnosis of either
25 OA or RA could be enrolled and were only excluded if they

1 presented a contraindication for the use of the study drugs,
2 specifically a history of recent or active GI disease or any
3 other comorbidities, such as serious renal or hepatic
4 disease.

5 [Slide.]

6 In keeping with this being a real world study, low
7 dose aspirin use was permitted. Again, cardiovascular
8 disease is common in the arthritis patient population. In
9 addition, patients were allowed to use antacids on a limited
10 basis, predominantly calcium supplements for osteoporosis.

11 They were prohibited, however, from using any
12 anti-ulcer drugs, either H2 receptor antagonists or proton
13 pump inhibitors because of their propensity to either mask
14 symptoms or alter the outcomes of interest. In addition,
15 patients were also not allowed to take NSAIDs during the
16 trial.

17 The treatments employed were celecoxib at the dose
18 of 400 mg twice daily, again, 2 times the RA dose and 4
19 times the OA dose, which were maximally effective, and the
20 doses of the comparators were 75 mg twice daily of
21 diclofenac, a commonly used dose for the indications in the
22 trial, and ibuprofen, 800 mg three times daily, again a
23 commonly used dose of ibuprofen for OA and RA.

24 [Slide.]

25 The trial power calculation was based on ulcer

1 complication rates of 0.3 events per 100 patient years for
2 celecoxib and 1.2 events per 100 patient years for NSAIDs.

3 Additional assumptions were that these incidence
4 rates would remain constant over time and that aspirin use
5 would approximate that seen within the context of the NDA,
6 approximately 12 percent.

7 The trial was powered to include a total of 40
8 events, requiring the enrollment of 8,000 patients, 4,000 on
9 celecoxib and 4,000 on the NSAIDs, 2,000 per each
10 comparator.

11 [Slide.]

12 In terms of the analysis plan, the endpoints to be
13 analyzed were ulcer complications, as well as symptomatic
14 ulcers and ulcer complications. The statistics were based
15 on an intent-to-treat analysis and included all patients who
16 took at least one dose of study medication.

17 The principal statistical test was the log-rank
18 test of time-to-event, and a step-wise comparison was
19 planned in which celecoxib was compared to the NSAIDs
20 combined and then to each NSAID separately.

21 [Slide.]

22 Risk factors prespecified in the protocol included
23 aspirin use, as well as the risk factors defined by the
24 previously performed MUCOSA trial, as well as a variety of
25 other risk factors which Dr. Geis discussed.

1 [Slide.]

2 There were three oversight committees which
3 supervised the performance of the trial.

4 [Slide.]

5 The committees and their membership are shown in
6 this slide. They consisted of the GI Events Committee
7 chaired by Dr. Goldstein and his colleagues; the Data Safety
8 Monitoring Board chaired by Dr. Faich and his colleagues,
9 and the Executive Committee chaired by Dr. Silverstein and
10 his colleagues.

11 [Slide.]

12 Their charters are simplified in this slide. In
13 brief, the GI Events Committee was to review all potential
14 GI events reported during the conduct of the trial.

15 The Data Safety Monitoring Board monitored the
16 accrual of such events and in addition performed the safety
17 oversight function looking at general safety during the
18 execution of the trial.

19 The Executive Committee was the main oversight
20 body and administered study conduct.

21 [Slide.]

22 I would like to review for you in some detail now
23 how information was funneled into the GI Events Committee
24 and then judged by the committee.

25 Investigators were asked to monitor for the signs

1 or symptoms of ulcer complications, which included but were
2 not limited to such symptoms and signs as dyspepsia,
3 abdominal pain, the presence of anemia or melena.

4 If any were present, they were asked to evaluate
5 the patient according to their ordinary clinical care
6 patterns, but they were required or asked to obtain at a
7 minimum stool testing for occult blood, hematocrit and
8 hemoglobin, as well as perform vital signs for determination
9 of volume status, and if indicated, they were to perform an
10 endoscopy or contrast radiographic study.

11 Clinical care was dictated as appropriate for the
12 work-up and the results obtained.

13 [Slide.]

14 All the information obtained by the investigators
15 was reported to the GEC or GI Events Committee.

16 [Slide.]

17 The GI Events Committee reviewed all such reports
18 and either diagnosed them as an ulcer complication, a
19 symptomatic ulcer, or assigned to them some other diagnosis
20 other than those two.

21 [Slide.]

22 Ulcer complications were prospectively defined in
23 the protocol as either bleeding ulcers, perforated ulcers,
24 or ulcers causing gastric outlet obstruction, and in this
25 trial, all ulcer complications required hard documentation,

1 that is, endoscopic or radiographic proof of an evidence of
2 an ulcer or a large erosion.

3 [Slide.]

4 Upper GI bleeding ulcers were the most common
5 complication and were subcategorized into four categories
6 again as prespecified by the protocol. Each category
7 required the presence of a lesion.

8 There was either hematemesis with the lesion or
9 the lesion demonstrated either active bleeding or evidence
10 of recent bleeding, the presence of melena with the lesion,
11 or the presence of blood in the stool by hemoccult testing
12 along with some clinical evidence of substantial blood loss.

13 [Slide.]

14 Symptomatic ulcers were also defined in the
15 protocol as any mucosal break with unequivocal depth found
16 on a "for cause" work-up, that is, a work-up performed to
17 investigate either a sign or a symptom of a potential ulcer
18 complication. Again, all ulcer complications required hard
19 documentation, that is, either endoscopic or radiographic
20 documentation.

21 [Slide.]

22 I would like now to share with you the results of
23 the trial, and I would like to direct my remarks first to GI
24 outcomes and then to general safety outcomes.

25 In discussing with you the GI outcomes, I would

1 first like to describe the study population, the GI
2 outcomes, and then potential sources of bias that may arise
3 in assessing ulcer complications.

4 After discussions with the agency, we will focus
5 today's discussion entirely on the entire study results as
6 opposed to the six-month analyses that have been presented
7 in the briefing documents.

8 [Slide.]

9 The demographics of the study population are shown
10 here. Patients averaged 60 years in age and were
11 predominantly female with the ethnic distribution as shown.
12 Seventy percent of the patients had a primary diagnosis of
13 OA and 30 percent a primary diagnosis of RA. No differences
14 were seen between the treatment groups.

15 [Slide.]

16 In terms of the risk factors as defined by the
17 MUCOSA trial, approximately 11 to 12 percent of patients
18 were either 75 years or older, 1.5 percent had a prior
19 history of GI bleed, and approximately 8 percent had a prior
20 history of ulcer disease. Forty percent of the patients had
21 a history of cardiovascular disease, again reinforcing my
22 comment that cardiovascular disease is a common comorbidity
23 in the arthritis patient population. No differences between
24 treatment groups were observed.

25 [Slide.]

1 Aspirin was used by approximately 22 percent of
2 the trial population, steroids were used by approximately 30
3 percent of the trial population, and anticoagulants, which
4 were permitted, were used by approximately 1 percent of the
5 trial population. No differences between treatment groups
6 again were apparent.

7 Although over-the-counter NSAIDs were prohibited
8 during the trial, approximately 5 to 6 percent of patients
9 in each of the treatment groups used such over-the-counter
10 NSAIDs, and in keeping with this being a real world clinical
11 trial, such patients were not removed from the protocol, but
12 were analyzed and kept within the study.

13 [Slide.]

14 Patients participated for a mean of approximately
15 7 months with a maximum exposure ranging between 12 and 15
16 months. Total exposure in the trial approximated 4,500
17 patient years split equally between celecoxib and the two
18 NSAID comparators.

19 [Slide.]

20 I would like to characterize for you individually
21 now the demographics of both the OA, as well as the RA
22 cohort contained within this trial. OT patients on average
23 tended to be slightly older than the overall study
24 population and were predominantly female. These patients
25 had long-standing OA of approximately 10 years in duration

1 and most had been on prior NSAID therapy up until the
2 inception of the trial. Again there were no differences
3 between treatment arms.

4 [Slide.]

5 The RA population within the trial tended to be
6 younger, was still predominantly female, but had long-
7 standing disease of approximately 10 years in duration.
8 Most had used NSAIDs prior to the trial, and approximately
9 50 percent used steroids and/or methotrexate during the
10 trial, and again there were no differences between treatment
11 arms.

12 [Slide.]

13 In terms of the disposition of patients,
14 approximately 50 percent or actually slightly less than 50
15 percent of patients completed the trial. Significantly,
16 fewer patients assigned to the ibuprofen arm completed the
17 trial compared to celecoxib patients.

18 More patients on diclofenac withdrew for adverse
19 events compared to the celecoxib-treated patients, and more
20 patients withdrew from the trial for treatment failure
21 assigned to ibuprofen relative to celecoxib. No patients
22 were lost to follow up that is, their medical status was
23 ascertained at the time they exited from the trial, so no
24 information is lacking because of lost to follow up
25 patients.

1 [Slide.]

2 So, to summarize, this was a representative cohort
3 of arthritis patients. Aspirin use was substantial,
4 approximately 1 in 5 patients used aspirin. No information
5 was lost because of lost to follow up patients.

6 Exposure to the study drugs was substantial and
7 ranged up to 15 months. Moreover, there was a higher
8 incidence of withdrawals seen from the study compared to
9 celecoxib, in ibuprofen-treated patients for treatment
10 failure, and diclofenac-treated patients for adverse events.

11 I would like now to discuss for you the GI
12 outcomes of the trial.

13 [Slide.]

14 During the trial, 1,500 cases of potential ulcer
15 complications were reported and each was evaluated by the
16 committee. Forty-four of these cases were diagnosed as
17 ulcer complications, 67 as symptomatic ulcers which did not
18 meet the definition of ulcer complication, and the balance
19 were assigned other diagnoses.

20 [Slide.]

21 In terms of the incidence of ulcer complications,
22 there was no difference in comparing celecoxib to the NSAIDs
23 combined as a group.

24 [Slide.]

25 In terms of the combined endpoint or the extended

1 endpoint, symptomatic ulcers and ulcer complications, there
2 was a significant difference observed between NSAIDs and
3 celecoxib with approximately a 40 percent reduction with a
4 p-value as shown.

5 [Slide.]

6 The Kaplan Meier curves which form the basis of
7 the prior bar graph are shown here. Again, there was a
8 linear accrual of events throughout the duration of the
9 trial with a p-value as shown here. This p-value is
10 obtained from the log-rank test of the time-to-event.

11 [Slide.]

12 Because the comparison with NSAIDs was
13 significant, we next compared with the individual
14 comparators. There was no significant difference between
15 celecoxib and diclofenac, but there was an approximately 2-
16 fold reduction in the incidence of symptomatic ulcers and
17 ulcer complications associated with celecoxib compared to
18 ibuprofen with a p-value as shown.

19 [Slide.]

20 The Kaplan Meier analysis of this bar graph is
21 shown here. Again, events accrued in a linear fashion
22 throughout the trial in both treatment arms with the
23 treatment difference being relatively easily apparent with a
24 p-value of 0.017.

25 [Slide.]

1 So, in sum, comparing celecoxib to NSAIDs as a
2 group, there was a lower incidence of symptomatic ulcers and
3 ulcer complications associated with celecoxib, and this was
4 also specifically true of the comparison of celecoxib to
5 ibuprofen.

6 [Slide.]

7 I would like to turn now to consideration of the
8 risk factors for such events.

9 [Slide.]

10 The prespecified risk factors are shown here and
11 are related either to the patients' characteristics, their
12 underlying disease, their concomitant medications, or prior
13 medical history.

14 [Slide.]

15 Risk factors which were significant in terms of
16 being associated with the outcome are symptomatic ulcers and
17 ulcer complication were age greater than or equal to 75
18 years, a prior history of ulcer disease or upper GI
19 bleeding, and cardiovascular disease.

20 Cardiovascular disease was a risk factor only by
21 virtue of its association with aspirin use. In addition,
22 aspirin use was shown to have a significant effect on
23 treatment outcome.

24 [Slide.]

25 Risk factors which were not significant are shown

1 here and included gender, alcohol or tobacco use, or disease
2 type or duration, or steroid use.

3 [Slide.]

4 So, this trial actually confirms the MUCOSA study
5 risk factor analysis, and additionally indicates that
6 aspirin use has an important effect on treatment outcome.

7 [Slide.]

8 Accordingly, we next analyzed the effect of
9 aspirin use by examining the outcomes in both the aspirin-
10 treated patients and the non-aspirin-treated patients.

11 [Slide.]

12 As shown here, there was no difference in the
13 incidence of symptomatic ulcers and ulcer complications in
14 patients on aspirin with the p-value as shown. There was,
15 however, a 2-fold reduction in the incidence of symptomatic
16 ulcers and ulcer complications in patients on celecoxib as
17 compared to NSAIDs combined with a p-value of 0.02.

18 [Slide.]

19 Turning now specifically to the comparison of
20 ibuprofen to celecoxib, there was no difference in the
21 incidence symptomatic ulcers combined with ulcer
22 complications in aspirin users, but there was an
23 approximately 2- to 3-fold reduction in non-aspirin users,
24 this value being significant with a p-value of less than
25 0.001.

1 [Slide.]

2 This Kaplan Meier curve shows the analysis of the
3 non-aspirin users comparing celecoxib to ibuprofen. Again,
4 events accrued linearly with time over the course of the
5 trial, and the treatment difference is readily apparent with
6 a p-value based on the log-rank test as shown.

7 [Slide.]

8 The profound effect of aspirin in terms of the
9 analysis of GI outcomes is shown in this graph. If one
10 looks at the primary outcome, that is, ulcer complications,
11 and compares celecoxib to ibuprofen, there is a 2- to 3-fold
12 reduction in the incidence of such comparing the two
13 treatment arms, the p-value for this comparison being 0.037.

14 [Slide.]

15 So, in conclusion, among non-aspirin users, there
16 is a lower incidence of symptomatic ulcers and ulcer
17 complications in patients on celecoxib compared to those on
18 NSAIDs and ibuprofen specifically, whereas, there is no
19 difference apparent within the context of aspirin use.

20 [Slide.]

21 Part of the robustness of this trial is that it
22 allows us to look at both RA and OA separately, and this is
23 a question, of course, which is of interest to
24 practitioners, that is, how do these drugs perform in these
25 different patient populations.

1 [Slide.]

2 In separating out the results for RA and OA,
3 comparing NSAIDs to celecoxib, two conclusions can be drawn
4 here. One is that the overall rates for each of the
5 treatment arms is similar between the two arthritides.

6 Additionally, the treatment effect within each
7 type of arthritis is similar. This was statistically
8 significant within the context of RA with a p-value of 0.04
9 and approached statistical significance within the context
10 of OA.

11 [Slide.]

12 We can also look at this comparison within the
13 context of patients not using aspirin. As shown here, in RA
14 patients not using aspirin, there is an approximately 2-fold
15 reduction in the incidence of symptomatic ulcers and ulcer
16 complications, this value being significant, and an
17 approximately 2-fold reduction in OA, this p-value
18 approaching significance.

19 Again the incidence of ulcer complications and
20 symptomatic ulcers between the two types of arthritis is
21 relatively similar.

22 [Slide.]

23 Turning now to a specific comparison between
24 celecoxib and ibuprofen, one sees similar results. The OA
25 and RA results for symptomatic ulcers and ulcer

1 complications for each of the treatment arms is quite
2 similar between the two different types of arthritis, and
3 the treatment differences or treatment effects are similar.
4 This approached statistically significance within the OA
5 cohort with a p-value of 0.11, and was significant within
6 the RA cohort with a p-value of 0.017.

7 [Slide.]

8 Among non-aspirin users, there was a 2- to 3-fold
9 reduction in the incidence of symptomatic ulcers and ulcer
10 complications in OA patients with a p-value as shown, and a
11 3- to 4-fold reduction in the context of RA with a p-value
12 as shown.

13 [Slide.]

14 This last bar graph is shown as a Kaplan Meier
15 analysis. Here again, for the non-aspirin cohort of RA
16 patients, as you can see here, events accrued literally over
17 time during the trial, and the treatment effect is readily
18 apparent with a p-value of less than 0.001.

19 [Slide.]

20 So, in sum, in comparing OA to RA, the incidence
21 of symptomatic ulcers and ulcer complications is similar
22 between the two types of arthritis. Moreover, the treatment
23 differences between celecoxib and NSAIDs, or celecoxib and
24 ibuprofen, are similar in the two types of arthritis.

25 [Slide.]

1 This trial taught us a lot about outcome trials
2 and potential sources of bias in assessing the endpoint of
3 ulcer complication.

4 [Slide.]

5 One such source of bias was the use of low dose
6 aspirin, and that I have outlined for you in detail
7 previously. Another potential source of bias that can enter
8 into such trials with respect to determining the rate of
9 ulcer complication is the withdrawal of patients with
10 symptomatic ulcers.

11 [Slide.]

12 Now, GI outcome trials, such as CLASS, assumed
13 that after treatment initiation, the patients would go on to
14 develop an ulcer complication and be withdrawn from the
15 trial as an event.

16 [Slide.]

17 However, if patients develop an earlier form of
18 the disease, which can be found by investigators, and
19 identified, leading to their removal from the trial, they
20 will lower the rate of ulcer complications observed.

21 Now, this source of bias will only be important if
22 there is differential withdrawal for symptomatic ulcers
23 between treatment arms, and as you can see in the next
24 graph, withdrawal for symptomatic ulcers alone was
25 significantly greater among patients treated with NSAIDs

1 than celecoxib. This differential withdrawal then can
2 introduce bias in the assessment of ulcer complication
3 incidence.

4 [Slide.]

5 So, in sum, celecoxib is associated with lower
6 incidence of symptomatic ulcers alone compared to NSAIDs,
7 and the withdrawals for such may bias the analysis of ulcer
8 complications in a trial such as this.

9 [Slide.]

10 I would like to turn now to consideration of
11 general safety and summarize my comments into either a
12 consideration of overall safety, an analysis of safety
13 specifically focused on the four body systems shown here, an
14 analysis in aspirin users, and an analysis of patients of
15 all ages particularly focusing on patients who are over 65
16 years of age.

17 [Slide.]

18 In terms of overall safety, deaths occurred
19 uncommonly during the trial and were large due to
20 cardiovascular disease because cardiovascular disease is a
21 common cause of morbidity and mortality in this patient
22 population.

23 Serious adverse events, those leading to
24 hospitalizations, occurred in approximately 10 cases per 100
25 patient years of exposure. There were no differences

1 between treatment groups either in deaths or serious adverse
2 events.

3 That was also specifically true of cardiac serious
4 adverse events or all-cause GI serious adverse events, which
5 includes a large subset of events not restricted to the
6 outcomes of the trial, such as esophageal, colonic, or
7 pancreatic serious adverse events.

8 There were no serious dermatologic adverse events
9 noted in patients assigned to celecoxib, and they occurred
10 infrequently among the other treatment arms. Renal serious
11 adverse events were also rare and consisted largely of renal
12 calculi.

13 [Slide.]

14 The common adverse events which occurred during
15 the trial are shown in the following two slides.

16 Common adverse events were significantly more
17 common in patients assigned to diclofenac than to celecoxib,
18 principally for those related to the GI system - dyspepsia,
19 abdominal pain, diarrhea, nausea shown here.

20 [Slide.]

21 Rash was more common among patients assigned to
22 the celecoxib-treated arm, but anemia, and peripheral edema
23 were more common among patients assigned to the ibuprofen-
24 treated relative to celecoxib.

25 Again, constipation as a GI side effect was more

1 frequently seen in patients assigned to diclofenac, and
2 elevated transaminases in specific ALT was seen more
3 frequently in patients assigned to diclofenac.

4 [Slide.]

5 Adverse events causing withdrawal were
6 significantly more common in patients assigned to diclofenac
7 compared to celecoxib. This difference was largely driven
8 by withdrawals due to GI events, such as abdominal pain and
9 nausea or, or hepatic events, such as elevated transaminases
10 as shown here.

11 [Slide.]

12 So, in summary, celecoxib appeared to be well
13 tolerated at this super-therapeutic dose as compared to the
14 NDA database that has been reviewed previously. In
15 addition, no dose- or duration-related increases in adverse
16 events were seen with the exception of non-serious rash
17 during the course of the course of the CLASS trial.

18 [Slide.]

19 I would like to now focus on the GI system. In
20 terms of GI adverse events, any cause adverse event was
21 significantly more common in patients assigned to diclofenac
22 compared to celecoxib, and this difference was largely
23 driven by the common GI adverse events shown here -
24 dyspepsia, abdominal pain, nausea, diarrhea and
25 constipation.

1 The clinical relevance of this difference in
2 tolerability is shown by the significant difference in
3 withdrawals. Withdrawals were significantly more common in
4 patients assigned to diclofenac as compared to those
5 assigned to celecoxib.

6 [Slide.]

7 The protocol also prespecified a definition of
8 what was considered to be a clinically significant decrease
9 in hematocrit or hemoglobin. Any decrease in hematocrit of
10 greater than or equal to 10 percentage points, or hemoglobin
11 greater than 2 grams per deciliter, was defined as being
12 clinically significant.

13 In terms of the incidence of such decreases, they
14 were significantly more frequent on both treatment arms as
15 compared to patients assigned to celecoxib, that is, they
16 are more frequent among NSAID-treated patients.

17 This was not simply a function of overt bleeding
18 due to ulcer bleeds because if you remove patients with
19 ulcer bleeds from the analysis, the incidence of such
20 significant changes in hematocrit and hemoglobin were still
21 significantly more common in patient on NSAIDs as compared
22 to patients on celecoxib.

23 [Slide.]

24 These decreases in hematocrit and hemoglobin were
25 associated with decreases in iron stores as indicated by the

1 iron/iron binding capacity. As shown here, these ratios
2 tended to decrease in diclofenac- and ibuprofen-treated
3 patients relative to patients on celecoxib.

4 [Slide.]

5 So, in conclusion, celecoxib appeared to be
6 associated with a lower incidence of GI adverse events and
7 withdrawals for such relative to diclofenac, and a lower
8 incidence of clinically significant reductions in hematocrit
9 and hemoglobin relative to both NSAID comparators.

10 Moreover, the decrease in iron stores that were
11 associated with such decreases suggests and are consistent
12 with chronic GI blood loss occurring with the NSAID
13 comparators.

14 [Slide.]

15 In terms of renal adverse events, overall renal
16 adverse events were significantly more common in patients
17 assigned to ibuprofen compared to celecoxib. This
18 difference was attributable to a significantly higher rate
19 of hypertension, generalized or peripheral edema in patients
20 on ibuprofen.

21 [Slide.]

22 Also, in the protocol, there was predefined
23 definition of clinically significant renal lab
24 abnormalities. That consisted of any patient who exhibited
25 serum or urea nitrogen or BUN of greater than or equal to 40

1 mg percent, or a creatinine greater than or equal to 1.8 mg
2 percent.

3 Such clinically significant abnormalities were
4 significantly more common in patients assigned to diclofenac
5 as compared to patients assigned to celecoxib.

6 [Slide.]

7 So, in sum, celecoxib appeared to be associated
8 with a lower incidence of hypertension and edema compared to
9 ibuprofen, and a lower incidence of clinically significant
10 increases in creatinine and/or BUN than diclofenac.

11 [Slide.]

12 In terms of hepatic issues, this graph show the
13 protocol-defined clinically significant elevations in
14 hepatic transaminases, those that were 3 times the upper
15 limit of normal.

16 Such elevations occurred in approximately 3 1/2
17 percent of patients treated with diclofenac consistent with
18 the known hepatotoxic potential of diclofenac. This was
19 significantly and substantially greater than the rates seen
20 in patients assigned to celecoxib.

21 Withdrawals for such transaminase elevations were
22 commensurate, that is, approximately 3 1/2 percent of
23 patients withdrew from the trial for such elevations in
24 patients assigned to diclofenac, and that was commensurately
25 reduced in the patients assigned to celecoxib.

1 [Slide.]

2 So, celecoxib was clearly associated with a lower
3 incidence of clinically significant increases in
4 transaminases relative to patients assigned to diclofenac.

5 [Slide.]

6 Turning to the cardiovascular system,
7 thromboembolic events in the trial were seen with equal
8 frequency on all three treatment arms. That was true for
9 any arterial or venous thromboembolic event or specifically
10 true for the four major cardiac thromboembolic events - MI,
11 angina, coronary artery disease, or unstable angina.

12 Stroke actually was seen significantly less
13 commonly among patients assigned to celecoxib compared to
14 those assigned to ibuprofen.

15 [Slide.]

16 Now, in consideration of patients not treated with
17 aspirin, of course, is important because these represent
18 patients potentially at risk for such complications,
19 however, no treatment differences were observed between the
20 treatment arms in the CLASS study even among this cohort for
21 any thromboembolic event or specifically for MI, angina,
22 CAD, or unstable angina.

23 Stroke again was significantly less common in
24 patients assigned to celecoxib relative to diclofenac.

25 [Slide.]

1 Atrial dysrhythmias are shown in this slide.
2 Atrial fibrillation was the most common atrial dysrhythmia
3 observed in this patient population, again consistent with
4 this being an older patient population. No treatment
5 differences were observed for this arrhythmia or any of the
6 other atrial arrhythmias observed or shown eh re.

7 Congestive heart failure was rare during the trial
8 and it occurred with equal frequency in all three treatment
9 arms.

10 [Slide.]

11 Looking specifically again at patients not treated
12 with aspirin, the incidence of atrial fibrillation was low
13 and not different between treatment arms, and other atrial
14 dysrhythmias were rare.

15 Congestive heart failure also was rare within the
16 study, and not different between all three treatment arms,
17 but withdrawals for congestive heart failure were
18 significantly more common in patients treated with ibuprofen
19 compared to patients treated with celecoxib.

20 [Slide.]

21 So, overall, comparing celecoxib to both the NSAID
22 comparators, there was no difference in thromboembolic
23 events observed and no difference in the incidence of atrial
24 dysrhythmias or congestive heart failure.

25 The GI protective effect in terms of the GI

1 outcomes of the trial were predominantly seen within the
2 context of non-aspirin users. It is an important issue for
3 clinicians and an important aspect of this trial to analyze
4 what the safety profile is in the context of aspirin use.

5 [Slide.]

6 As shown here, selectively in aspirin users, any
7 GI adverse event and withdrawals for such were more common
8 among patients treated with diclofenac compared to those
9 with celecoxib, this difference being significant for
10 withdrawals.

11 Renal events again were significantly more common
12 in patients treated with ibuprofen relative to celecoxib.
13 Again this is within the aspirin using population.

14 [Slide.]

15 Although aspirin increased the incidence of
16 clinically significant changes in hematocrit and hemoglobin
17 in all three treatment arms, the treatment differences were
18 preserved, that is, there were fewer such decreases in
19 patients treated with celecoxib as compared to those treated
20 with either diclofenac or ibuprofen.

21 [Slide.]

22 In terms of clinically significant renal
23 abnormalities, that is, increases in renal function tests,
24 they tended to be higher among aspirin users consistent with
25 this patient population having a higher incidence of

1 cardiovascular disease, but the treatment difference between
2 diclofenac and celecoxib was preserved and was significantly
3 different between these two treatment arms.

4 [Slide.]

5 Hepatotoxicity was evident regardless of the use
6 of aspirin, and the treatment differences between diclofenac
7 and ibuprofen were preserved and substantial.

8 [Slide.]

9 So, in sum, even among aspirin users, the general
10 safety profile is quite similar to the patients not on
11 aspirin with respect to GI, renal, and hepatic safety.

12 [Slide.]

13 It is particularly important to look at safety
14 within the context of the older patient, because the
15 arthritis patient population tends to be older, and this
16 slide summarizes for you in very brief form the safety in
17 patients who are 65 years or older.

18 [Slide.]

19 GI adverse events again occurred significantly
20 more commonly in patients assigned to diclofenac. Decreases
21 in hematocrit and hemoglobin were also significantly more
22 common in patients assigned to either of the two NSAIDs
23 comparators compared to diclofenac.

24 Overall renal adverse events were significantly
25 more common again in patients treated with ibuprofen, and

1 increases in renal function tests were significantly more
2 common in patients treated with diclofenac. Hepatotoxicity
3 was even more apparent within this older patient population,
4 and again, there was a significant and substantial
5 difference between patients treated with diclofenac and
6 celecoxib.

7 [Slide.]

8 So, the safety profile of celecoxib appears to be
9 maintained even within the older population.

10 The following two slides will then summarize all
11 the comments that I have made in graphical form.

12 [Slide.]

13 The GI safety advantages of celecoxib, which are
14 largely mechanism, that is, COX-2 based, are shown here.
15 Celecoxib was associated with a significantly decreased
16 incidence of symptomatic ulcers and ulcer complications
17 versus NSAIDs combined and ibuprofen specifically.

18 Celecoxib was associated with less chronic GI
19 blood loss versus NSAIDs combined or either of the two
20 comparators, and associated with fewer GI adverse events
21 versus both NSAIDs combined and diclofenac specifically.

22 Blood loss and tolerability differences were also
23 evident within aspirin-using patients.

24 [Slide.]

25 In terms of general safety attributes, which may

1 develop methods to control bleeding using lasers and heated
2 monopolar and a variety of techniques.

3 I spent about a decade of my life doing that with
4 Dr. David Auth, but then I realized in the early eighties
5 that I didn't really know who was bleeding, and so we did a
6 large study with the ASGE looking at the demographics of
7 what patients were bleeding.

8 It was just at this time that this association
9 with NSAIDs was becoming clear and then I got involved in
10 understanding that and in looking at protective agents and
11 specifically prostaglandins. Then, we did the MUCOSA trial,
12 which kind of put these things together a big, and then I
13 was privileged to be able to work with the COX-2 inhibitors,
14 but I am telling you we know so much more now than we did in
15 1963, when I started in medical school about what causes
16 ulcers.

17 Almost everything we thought then was wrong, what
18 caused them, how to diagnose them, what to do about them,
19 and things have really progressed with the H. pylori
20 hypothesis and with the understanding of the importance of
21 nonsteroidal agents. So, I think it has just been a truly
22 remarkable advance in our knowledge, and I think the
23 advantages of the COX-2 inhibitors are really pretty
24 apparent.

25 Could I have Slide 1141, please.

1 [Slide.]

2 So, I would just like to briefly summarize what I
3 take away from what I just heard as a consultant clinical
4 investigator from Seattle to Searle.

5 The first has to do with the trial design. This
6 was a truly rigorously designed trial. It was blinded. I
7 chair the Executive Committee. I guarantee the blind was
8 never broken, not once. We had no idea what groups patients
9 were in or what medication the patients were on.

10 It was a randomized, blinded trial, and really the
11 people who deserve the most credit are the patients who
12 donated all of their effort to being part of the trial,
13 along with the physicians, the nurses, the clinical research
14 associates, et cetera, but I think it was a remarkable
15 effort, and it has resulted in a huge database of very
16 robust data, and I think the agency's analysis of the study
17 agrees with that, that this is a very well done study with
18 some really good data that we can use.

19 Of interest to me, we designed the study using the
20 safest NSAIDs as comparators with ibuprofen and diclofenac
21 at doses of celecoxib which were higher than at 2X or 4X,
22 the approved dose of celecoxib for the intended population,
23 whereas, the NSAIDs were used at the routine dose.

24 We didn't allow proton pump inhibitors or H2
25 blockers which might have masked symptoms, and kept people

1 in the trial until they developed a complication as opposed
2 to saying, hey, she is symptomatic, she was endoscoped, she
3 had an ulcer, she is coming off the trial before she
4 developed a complication.

5 And we allowed aspirin, which I think is critical
6 because you have already seen that it has a dramatic effect,
7 and I think it is an important part of a study of this type.

8 So, I think it is an excellent trial design.

9 To look at the clinical results of the trial, I
10 would like to turn to Slide 257, please.

11 [Slide.]

12 So, what was presented here was the ulcer
13 complication rate in all the patients, had a trend in the
14 right direction, but was not quite statistically
15 significant. When the patients who were taking aspirin were
16 taken out of the analysis, the change was more apparent.

17 What I am going to address in the next just few
18 minutes is what happened, you know, what happened to the way
19 we planned the trial versus the way the trial turned out,
20 and one of the key things is that nothing happened to the
21 celecoxib group.

22 The celecoxib group basically did what it was
23 predicted to do. It had, off of aspirin, it had about a 0.4
24 percent complication rate. That wasn't the issue. The
25 issue was why did the comparator nonsteroidals have a lower

1 rate, which is what created this question about why the
2 primary endpoint wasn't quite achieved.

3 Could I have 256, please.

4 [Slide.]

5 So, when we look at the primary endpoint was this
6 ulcer complication endpoint, and then as you heard in Dr.
7 Lefkowitz's presentation, the symptomatic ulcers were added
8 to that. This was an endpoint, a secondary endpoint, which
9 was identified prospectively in the protocol, and it seems
10 to me to make sense to combine them.

11 Now, Dr. Geis, in that lovely tutorial on ulcers
12 and NSAIDs, showed us that the difference between a
13 complicated ulcer. So, when we combined the symptomatic
14 ulcer, the question is should we be looking at a meaningful
15 endpoint of combining the symptomatic ulcers, and from my
16 clinical standpoint, I would say absolutely we should.

17 Steve showed us that the difference. I have
18 endoscoped thousands of patients and hundreds, as many of
19 you have, of bleeding patients, and the difference between a
20 patient who has a ulcer and a patient who has a bleeding
21 ulcer, a complicated ulcer, is really a temporal phenomenon
22 in some cases, and I think it does make sense from a
23 clinical standpoint to combine those two as another
24 endpoint, an alternative endpoint.

25 Now, could I have Slide 124, please.

1 [Slide.]

2 Now, the question then is, well, what happened. I
3 mean this was an evidence-based trial in terms of design.
4 We took this huge amount of data from the MUCOSA trial, from
5 the literature, et cetera, and designed the trial.

6 The question was, well, what happened. Well,
7 things happen, and what happened was that there were changes
8 in several aspects of the way patients were entered into the
9 trial and managed on the trial.

10 What do I mean? Well, in the MUCOSA trial, as Dr.
11 Lefkowitz pointed out, we identified four risk factors as
12 being important for increased likelihood of a complication,
13 and you can see the incidence of each of those factors.

14 But look what happened in the CLASS trial. They
15 went down. There were fewer people with these risk factors
16 entered in the CLASS trial, and that just reflects clinical
17 practice. Practitioners are smart, they read the
18 literature, they know these people are at risk, and they
19 tend to change the nature of the people they will put on a
20 clinical trial.

21 So, the first factor was that there was a change
22 in the underlying risk of the patients in the CLASS trial,
23 which had not been prospectively anticipated.

24 May we have 126, please.

25 [Slide.]

1 Now, the second factor was the use of aspirin, and
2 here I am comparing the NDA database in which 12 percent of
3 people were on aspirin, as I believe Steve mentioned
4 earlier, and in the CLASS trial, where 22 percent of
5 patients were on aspirin, and this probably, once again,
6 reflects changes in clinical practice, more people in the
7 older population being put on aspirin prophylaxis. Whether
8 that is the right thing to do or not for primary prophylaxis
9 is yet another issue.

10 But clearly, again, the CLASS trial had this
11 factor, which was almost twice as large numerically as the
12 NDA data, and as we have seen from the data that Dr.
13 Lefkowitz showed us, had a very significant impact on
14 outcome.

15 Can we have 126, please.

16 [Slide.]

17 The third factor I want to show you, of multiple
18 factors we could talk about, has to do with how many
19 patients were worked up from a GI standpoint.

20 In the MUCOSA trial, which was a huge body of
21 work, about 2.7 percent of people were worked up for
22 abdominal symptoms to determine if they had an ulcer, et
23 cetera, but in the CLASS trial, this almost doubled to 4.8
24 percent.

25 Now, what that means clinically is that patients

1 were presenting with symptoms, they were being endoscoped
2 for cause, and if they had an ulcer, they were being taken
3 off the trial as a symptomatic ulcer, and for the reasons
4 that Steve showed you, I believe, as he does, that ulcers
5 become complicated ulcers. If you take an ulcer out of the
6 trial, that ulcer cannot become a complicated ulcer. So,
7 that is another change that occurred that could not have
8 been discerned from the MUCOSA trial, but did occur in the
9 CLASS trial.

10 122, please.

11 [Slide.]

12 The final slide is looking at the data using the
13 combined endpoints saying ulcer complications are important,
14 we told you what happened with that, but symptomatic ulcers
15 are important, too, and when you combine then and you look
16 at all patients, you see the difference that occurred with
17 celecoxib, and especially when you take the aspirin patients
18 out, you see an even more remarkable difference in the
19 reduction from NSAIDs to celecoxib for the combined
20 endpoint.

21 Once again this is what we expected. We did
22 expect this type of data with celecoxib. It was rather the
23 comparators that were the issue.

24 So, can we go back, please, to Slide 1141.

25 [Slide.]

1 And so in conclusion, I would say that there is a
2 large body of data about celecoxib and the GI tract. There
3 are about 60 controlled trials in about 25,000 patients.
4 There is a large body of data that I think suggests that
5 there is improved GI safety in terms of GI symptoms,
6 withdrawal for GI symptoms, complications symptomatic
7 ulcers, et cetera.

8 I think that, therefore, the CLASS trial actually
9 confirmed the antecedent trials with the notes that I made
10 about why there were some differences.

11 The safety data from the CLASS trial, which is
12 also a large body of data, also found no new signals. There
13 was not evidence of cardiovascular or renal effects, and it
14 looks as if celecoxib is not any worse than NSAIDs, and in
15 some ways may be somewhat better.

16 So, again, we have expanded this large safety
17 database, and we are not finding any signals of
18 unanticipated adverse events.

19 [Slide.]

20 So, in conclusion the NSAID problem is a large
21 problem. The gastroenterologists and the rheumatologists
22 didn't agree about this for a couple of decades because they
23 were saying, hey, it's only 1 percent, I have 300 in my
24 panel, and only seen one or two events a year.

25 The gastroenterologists were saying that is crazy,

1 half the people I see coming in bleeding are on NSAIDs.

2 So that has become resolved as we have understood
3 these numbers, but if there are 15 or 17 million people on
4 NSAIDs in the United States, and a 1 percent incidence of
5 that is 150,000 to 170,000, it is a lot of people, and if we
6 can cut that in half, then, you have saved 50- or 100,000 of
7 these bleeding episodes.

8 So, even though the incidence is small, because of
9 the population exposed is so large, it is a major problem.
10 So, what I would include is that the data from the CLASS
11 trial supports the fact that celecoxib is a safe and
12 effective drug and is well tolerated, and I think is a real
13 addition to our armamentaria for patients with arthritis.

14 Thank you.

15 DR. HARRIS: Thank you very much, Dr. Silverstein.

16 I am going to just ask now if there are any
17 questions of clarity that one may want to ask any of the
18 sponsors by any member of the committee? Yes.

19 DR. PINA: I have a whole series of questions
20 actually.

21 Of the whole 40 patients that had a cardiovascular
22 history, how many of those were the aspirin users? You have
23 22 percent on aspirin at entry and 40 percent of patients
24 with a cardiovascular history, are the 22 percent part of
25 that 40 percent?

1 DR. LEFKOWITH: In using the guidelines, the FDA
2 guidelines for what is appropriate secondary prophylaxis,
3 approximately, 16 percent of the patients, that is 16
4 percent, not of the 22 percent, but 16 percent were taking
5 it for secondary prophylaxis and 6 percent were taking it
6 for other reasons.

7 DR. PINA: But were those part of the 40 percent
8 that had the cardiovascular history at entry?

9 DR. LEFKOWITH: Cardiovascular disease was defined
10 as any instance of cardiovascular disease. All patients
11 given it for secondary prophylaxis would have met that
12 definition of cardiovascular disease.

13 DR. PINA: I have another question if I may. You
14 don't talk about other concomitant use of drugs, and if you
15 have such a high number of patients with cardiovascular
16 disorders, I would think that among them, and many of them
17 hypertensives, there is a high use of ACE inhibitors in this
18 group.

19 Did you set aside the ACE inhibitor patients, do
20 you know how many patients were on ACE?

21 DR. GEIS: As part of the normal course of the
22 study, we did collect concomitant medications, and we can
23 provide you that data.

24 DR. LEFKOWITH: In terms of the use of ACE
25 inhibitors specifically, in incidence of patients who

1 entered the trial using ACE inhibitors is shown here. The
2 incidence of those starting ACE inhibitors during the trial
3 is shown here.

4 Does that answer your question?

5 DR. PINA: Well, it answers my question as far as
6 entry drug criteria, but I again start wondering about the
7 interactions of these drugs with patients on these
8 inhibitors, particularly with the renal effects, and I am
9 sure we will get to this a little bit later.

10 DR. HARRIS: Dr. Wolfe?

11 DR. M. WOLFE: I had a similar question. I was
12 really surprised at the number of patients on ibuprofen,
13 taking ibuprofen over the counter, as well, as well as
14 naproxen over the counter, and even though they were
15 instructed not to take H2 blockers or PPI's, were they
16 taking it either in prescription form or over the counter?

17 DR. GEIS: We can present that data. Dr.
18 Lefkowitz.

19 DR. LEFKOWITH: Prescription or over-the-counter
20 H2 blockers or PPI's?

21 DR. M. WOLFE: Prescription PPI's.

22 DR. LEFKOWITH: Prescription PPI's.

23 DR. M. WOLFE: Over the counter or prescription,
24 both.

25 [Slide.]

1 DR. LEFKOWITH: This is for NSAID use. You were
2 asking for PPI's or H2 blockers? I am sorry. You wanted
3 the PPI's and the H2 blockers. We will get that up in a
4 second.

5 Such use obviously did occur during the trial, and
6 patients were not excluded if they used it over the counter.
7 Prolonged use that was discovered during the trial of PPI
8 use or at prescription doses, however, did lead to patients
9 being removed from the trial as a protocol violation.

10 Could we have the slide, please.

11 [Slide.]

12 As you can see, this is an overwhelming list of
13 medications which taxes my visual acuity at this distance,
14 but maybe we can cone down in terms of H2 receptor
15 antagonists, the use was approximately 5 percent in the
16 trial population. I don't believe we show here any use of
17 PPI's. PPI's were used predominantly in the treatment of
18 events, but H2 receptor antagonists were used during the
19 trial by the patient population.

20 DR. HARRIS: Yes.

21 DR. WOFSY: I also have two questions relating to
22 thrombotic events, one in aspirin users and one in non-
23 aspirin users.

24 What was the thrombotic event rate in the aspirin
25 users? It seems that we had a lot in the non-aspirin users.

1 Do you have any data on the cardiovascular thrombotic event
2 rate in aspirin users compared to non-aspirin users?

3 DR. GEIS: Yes, we do. We can pull that slide.

4 DR. LEFKOWITH: Could we have the slide, please.

5 Now, the incidence of thromboembolic events in the
6 aspirin users is higher than non-aspirin users, which I
7 showed you during my talk. It's about 5 percent. That is
8 because, of course, the patients using aspirin are at risk
9 for cardiovascular events, that is why they are on aspirin,
10 but there were no treatment differences observed between
11 celecoxib and the NSAIDs for either any thromboembolic event
12 or the specific cardiac thromboembolic events that I showed
13 you or for stroke.

14 DR. WOFSY: And in non-aspirin users, the question
15 really has to do with statistical power. If I recall your
16 slide correctly, there was an increase that was not
17 statistically significant in the patients who were treated
18 with Celebrex.

19 Would you have been powered, at what level were
20 you powered to detect a statistically significant difference
21 in that area?

22 DR. GEIS: I would like to have Dr. Jerry Faich,
23 the head of our DSMB, respond to that question.

24 DR. FAICH: The short answer is that study was not
25 powered to detect such a difference. Later on perhaps we

1 can talk about--the best way to go at that, this is a study
2 of 2,000 person years of exposure to celecoxib, is to look
3 at a pooled analysis including the NDA and the open label
4 extension. Perhaps this afternoon would be a better time to
5 do it, but the short answer is there isn't a powered answer
6 to that question, but there wasn't a signal, I mean, so it
7 goes both ways.

8 DR. HARRIS: Dr. Cryor.

9 DR. CRYOR: With respect to this 5 to 6 percent
10 use of the over-the-counter NSAIDs, have you assessed how
11 that OTC NSAID use impacted your observations with respect
12 to ulcer complications or symptomatic ulcers?

13 DR. GEIS: Yes, we have. Dr. Lefkowitz will take
14 that.

15 DR. LEFKOWITH: We examined the profiles of all
16 the patients with ulcer complications for use of over-the-
17 counter NSAIDs just to understand the confounding effect
18 that it might have. There were three actually complications
19 in both the Celebrex-treated group, as well as the NSAID-
20 treated group, who used NSAIDs or over-the-counter NSAIDs
21 concomitantly.

22 Most of that use was sporadic and not temporally
23 related to the event. One patient assigned to the
24 celecoxib-treated arm was on salicylamide for a prolonged
25 period of time, at a time that was immediately proximate to

1 the event, and could have been related to an event. This
2 patient, however, was still included as a celecoxib event in
3 the analysis that I showed you.

4 DR. HARRIS: Dr. Sampson.

5 DR. SAMPSON: I understand that you did a pooled
6 analysis of the two different studies. It would be helpful
7 to see two slides, if you would have it, the patient
8 disposition and the adverse events causing withdrawal broken
9 separately by the two studies with the two different
10 Celebrex treatments, one for Study 035 and one for Study
11 102.

12 DR. GEIS: I believe we do have that data broken
13 out by study. We can pull the slide, and we can show that.

14 DR. LEFKOWITH: You wanted patient disposition
15 unblinded or blinded?

16 DR. SAMPSON: Your Slide No. 93 and the other one
17 would be 132.

18 DR. LEFKOWITH: Can I have the slide, please. I
19 am having trouble hearing you without the microphone.

20 [Slide.]

21 This is the disposition within the comparison
22 between celecoxib and ibuprofen in terms of completers and
23 withdrawals for adverse events, and I believe the next slide
24 is the same comparison between diclofenac and ibuprofen
25 within the trial, which again shows the same results as the

1 pooled results.

2 DR. SAMPSON: Do you have that, though, broken
3 down by study?

4 DR. GEIS: This analysis shows the celecoxib
5 pooled.

6 DR. SAMPSON: I want to see the celecoxib
7 separate. I am sorry if I did not make that clear.

8 DR. GEIS: We don't have it broken out in a slide,
9 but maybe this afternoon we can bring that back and we can
10 show you that, but we can get that.

11 DR. SAMPSON: That would also be for Slide 132,
12 which is adverse events causing withdrawals at a rate
13 greater than 1 percent?

14 DR. GEIS: And you want the adverse events causing
15 withdrawals by study with celecoxib separate in that study,
16 not pooled.

17 DR. SAMPSON: That is correct. Thank you.

18 DR. GEIS: We can pull that this afternoon, as
19 well.

20 DR. NISSEN: I would be interested in seeing the
21 myocardial infarction rates by drug, not pooling the other
22 NSAIDs, because ibuprofen, you know, these two drugs have
23 differing effects on platelets, so I would like to see the
24 celecoxib versus the other two agents compared with respect
25 to the myocardial infarction rate.

1 DR. GEIS: So, MI rate, celecoxib pooled versus
2 diclofenac, versus ibuprofen. Do we have that slide?

3 DR. LEFKOWITH: Can I have the slide, please.

4 This was the chart that I showed you, and I did
5 show a vast amount of data during the talk, but this slide
6 does have the MI rates broken out by treatment group. This
7 is for all patients. Now, of course, this includes both
8 aspirin users, as well as non-aspirin users.

9 DR. NISSEN: I meant in the non-aspirin users.

10 DR. LEFKOWITH: Okay. Could we have the next
11 slide, please.

12 This, of course, is an important comparison
13 because these patients are not protected by cardiovascular
14 aspirin. That rate was no different and quite low in all
15 three treatment arms.

16 DR. M. WOLFE: Along those lines, though, it is a
17 difficult question, is there a study or a breakout of the
18 patients with a previous history of an MI, who were not
19 treated with aspirin, yet, were treated with the other three
20 drugs?

21 DR. GEIS: So, the question is do we have it
22 broken out by patients with cardiovascular disease, a
23 history, who were not on aspirin, is that right?

24 DR. M. WOLFE: Yes.

25 DR. LEFKOWITH: Can I have the slide, please.

1 [Slide.]

2 So, in terms of MI's, again, now, you are talking
3 about ever smaller cohorts within the trial, so you have to
4 take these numbers in the context of being subanalysis, but
5 nonetheless, if you look at MI's on celecoxib in patients
6 not on aspirin, with a prior history of cardiac disease,
7 there were two infarcts in the celecoxib group compared to
8 one infarct in the NSAID group. Those rates are not
9 different.

10 DR. HARRIS: Any other questions?

11 [No response.]

12 DR. HARRIS: Okay. We will take a break. It's
13 10:15, and we will be back in 15 minutes.

14 [Break.]

15 DR. HARRIS: We would like to resume and in this
16 portion of our session, we are going to get a presentation
17 from the FDA. We will start with Dr. Lawrence Goldkind.

18 **FDA Presentation**

19 **GI**

20 **Lawrence Goldkind, M.D.**

21 DR. GOLDKIND: My name is Dr. Goldkind. I will be
22 reviewing some of the highlights of the gastrointestinal
23 review of the CLASS study.

24 [Slide.]

25 First, I will briefly review some of the study

1 design highlights, which will overlap some with the
2 presentation by Dr. Lefkowitz. Then, I will review some of
3 the results specifically the primary analysis as specified,
4 which was complicated ulcer.

5 The term CSUGIE is only here, it will be
6 reproduced a few times, but since the committee had received
7 documents littered with that term, we wanted to make it
8 clear. Complicated ulcer will be used in place of this term
9 which, for the rest of the audience, stood for a clinically
10 significant upper GI event, but they are identical for
11 purposes of this discussion.

12 The initial intent-to-treat population, and then
13 important subgroup analyses as have been discussed, aspirin
14 and non-aspirin, important for obvious reasons.

15 Then, I will discuss the composite endpoint, the
16 symptomatic ulcers combined with the complicated ulcers as
17 was eloquently described by Dr. Geis, again, the intent-to-
18 treat population and the subgroup analysis of aspirin users
19 and separately non-aspirin users.

20 [Slide.]

21 I will briefly discuss high risk populations and
22 make several concluding remarks.

23 [Slide.]

24 The original protocol stated that, "The null
25 hypothesis being tested is that there is no difference in

1 the incidence of clinically significant upper GI events"
2 between Celebrex and each of NSAID groups, ibuprofen and
3 diclofenac.

4 [Slide.]

5 Some highlights from the original statistical plan
6 stated that, "Two primary treatment comparisons will be
7 performed: celecoxib vs. ibuprofen and celecoxib vs.
8 diclofenac.

9 "A stepwise procedure will be used to strongly
10 control type 1 error. In this procedure, the first step is
11 to test the overall hypothesis whether celecoxib and the
12 pooled NSAIDs are different.

13 [Slide.]

14 "If the test is not significant, the null
15 hypothesis is retained and the procedure stops. If the test
16 is significant, the second step will be the pairwise tests
17 between celecoxib and each of the two NSAIDs."

18 So, it is clear that the intent was to compare
19 celecoxib to each NSAID, but to avoid issues related to
20 multiplicity and the need for statistical correction, a
21 stepwise approach was employed.

22 I will try and go through these briefly.

23 [Slide.]

24 The endpoint definition, perforation, obstruction,
25 and upper gastrointestinal bleeding. Through the vast

1 majority of this slide and the presentation by the sponsor,
2 a traditional definition as defined by the sponsor has been
3 employed which, as has been described, requires clear
4 evidence of blood loss with evidence of gastroduodenal
5 injury.

6 An alternate definition was used in addition for a
7 separate analysis just to get a look at more severe or
8 potentially imminently life-threatening bleeding that would
9 require gastroduodenal injury be documented along with signs
10 of an acute major bleed, which would include transfusion,
11 orthostasis, or a significant drop in hemoglobin of 2 grams
12 per deciliter.

13 [Slide.]

14 Again, using the traditional definition, this
15 required gastroduodenal ulcer or erosion in addition to one
16 of the following: hematemesis, active bleeding at the time
17 of endoscopy, stigmata of recent bleed, which we saw some
18 photos of earlier, and I will just make a point that in
19 these cases, again, the quantitation of bleeding wasn't
20 specified. Again, certainly these are very important
21 endpoints, but this is where the differentiation with the
22 more rigorous or severe bleeding definition, the alternate
23 definition is relevant.

24 [Slide.]

25 Melena, hemoccult-positive stool, and fall in