

1 DR. HARRIS: Thank you very much, Dr. Wolfe. I
2 neglected to mention that you are with the Public Citizen
3 Health Research Group.

4 DR. S. WOLFE: I do not have any conflict of
5 interest, as public speakers are supposed to announce. I am
6 sorry, I forgot to announce that.

7 DR. HARRIS: Are there any questions and any
8 clarification issues? Yes, there is one. Dr. Wolfe.

9 DR. M. WOLFE: We are not related is a
10 clarification. But I think the numbers you come up with are
11 incorrect. If you do the calculations, 0.4 percent of 4,000
12 is 16, not 160, I am pretty sure.

13 DR. S. WOLFE: Ten percent of 4,000 is 400.

14 DR. M. WOLFE: 0.4 percent is less than 1 percent.
15 One percent of 4,000 is 40.

16 DR. S. WOLFE: It's a 4-fold difference still,
17 though, right.

18 DR. M. WOLFE: Yes, I agree, but the numbers are
19 very, very different.

20 DR. S. WOLFE: Okay. Sorry for that.

21 DR. HARRIS: Thank you very much, Dr. Wolfe.

22 No one else registered for public comment, and if
23 there are no other comments from the committee, we will
24 adjourn and reconvene after lunch. There is a table
25 reserved for members of the committee.

1 We will reconvene at 1:00.

2 [Whereupon, at 11:45 a.m., the proceedings were
3 recessed, to be resumed at 1:00 p.m., this same day.]

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

[1:00 p.m.]

DR. HARRIS: In starting this afternoon's session, I want to remind members of the committee and advisors that when you speak, if you can give your name before you speak, since this is being transcribed, and once you have made your comment, to turn off your microphone.

Of course, I forgot. My name is Nigel Harris, and I just spoke.

We are going to start this afternoon's session with a short presentation from the sponsors to clarify some of the questions that were asked this morning just to show some additional data that might help in terms of our discussions this afternoon.

Thank you.

DR. GEIS: Dr. Steve Geis. Thank you, Dr. Harris for the opportunity to present the data.

During the final moments of the morning discussion, there were some numbers being talked about in terms of cardiovascular events, and we would just like to take the opportunity to present the data in a way, so we are all on the same playing field about it.

So, I would like to ask Dr. Jerry Faich, who is the chairperson of our Data Safety Monitoring Board, to present that data.

1 DR. FAICH: Mr. Chairman, thank you. I am Jerry
2 Faich. I am a pharmacoepidemiologist. I have a particular
3 interest in safety. What I thought I would do is just
4 review once again the cardiac events, so I need to look at
5 Slide 1128, please.

6 [Slide.]

7 These are the same data that Jim Lefkowitz
8 presented this morning. This is celecoxib, and this is
9 nonsteroidals combined, approximately 4,000 patients in each
10 arm of the study. This is all thromboembolic events, and I
11 would call your attention to MI.

12 This is a rate of 0.5 percent versus NSAIDs 0.4,
13 and unstable angina 0.3 and 0.2. Overall in the group it is
14 2.5 and 2.1. The n's here--and I think that is the
15 important thing, they are not shown here--is for celecoxib,
16 the n here is 20; for unstable angina the n is 12, the total
17 is 32. Over here, the n is 16 for NSAIDs, and 8, the total
18 is 24. So, those are the four numbers that go with these
19 four rates.

20 [Slide.]

21 In the non-aspirin exposed group, you see a much
22 lower number. It is 1.5 and 1.2. The rates are 0.2 and
23 0.1. Down here for unstable it is less than 1 and less than
24 1, and the n's here are 6 for MI and 2 versus 3 and 5. That
25 is, we are talking 8 versus 5, again, a small numbers

1 situation here without a lot of power.

2 Probably importantly, let me show you the Kaplan
3 Meier curves, the time-to-event on these n's.

4 [Slide.]

5 This is the combined MI and unstable angina. That
6 is the 32 I was just showing you. This top line is
7 celecoxib, and the combined NSAIDs are diclofenac and
8 ibuprofen, n of 24, and you can see here visually, and also

9 by log-rank testing that these are not significantly
10 different in either their pattern or in their n.

11 Of course, since this includes aspirin takers,
12 that is where all the MI's were occurring. When we look at
13 non-aspirin group, which is the Kaplan Meier sets, much
14 smaller numbers.

15 [Slide.]

16 Again it is 8 versus 5, but again the point being
17 there is no difference here. So, in looking at these data
18 in the aggregate, there does not appear to be any increase
19 in MI or unstable angina in the celecoxib patients.

20 If you like--this is the data, this is a review of
21 the data--I am happy to show you the pooled analysis which
22 combines these data with the NDA trial database and the open
23 label. Here, we are talking about 2,000 person years of
24 exposure to celecoxib. In the combined pooled data, it is
25 10,000 person years.

1 As I said earlier this morning, there is very
2 little power in this, and this study wasn't powered, but as
3 you go from 2,000 to 10,000, you get a substantial increase
4 in power. So, with your permission I am happy to show that
5 if you think this is an appropriate time to do so.

6 DR. HARRIS: Nigel Harris. Can I get a sense from
7 anyone? Would anybody else on the committee would like to
8 see some of that? You would? Yes.

9 DR. FAICH: It is critical data to address this
10 issue, so can I have Slide 1131.

11 [Slide.]

12 Once again, this is now a pooling of the entire
13 NDA database plus the open label extension plus the CLASS
14 trial, so we are looking at, in this slide, nearly 10,000
15 person years of celecoxib exposure compared to 2,738 patient
16 years of exposure to NSAIDs. This is all thrombotic events.

17 So, the line of interest that was parallel to what
18 I just showed you is this one. It is MI combined with
19 unstable angina and myocardial ischemia. There were 90 such
20 events. That turns into a calculated rate of 9.1 per 1,000
21 person years. In the NSAID group, there were 23. That is a
22 rate of 8.4. These are not significantly different. In
23 fact, two more patients over here would make these rates
24 identical.

25 Similarly, if you talk about angina and coronary

1 artery disease, this is a more stable phenomenon, probably
2 something different. The rates are quite similar. There is
3 no difference overall in this group except in the embolism
4 thrombophlebitis, there were actually fewer events and a
5 lower rate, and the same trend is there for CVA.

6 Overall, for these thrombotic events, the overall
7 rate is 34.3 versus 38.9, no difference. Now, the question
8 of power in this, this has sufficient power to rule out a 20
9 percent difference, and so that starts to be important, and
10 let me explain what I mean by that.

11 These data allow one to say that this 9 cannot be
12 higher than 11, that is, it rules out that level of
13 difference, so I can't tell you that there is less than a 20
14 percent difference between these, but I can say with some
15 degree of certainty and power that there is no more than a
16 20 percent difference. So, that is a substantial amount of
17 power, and I would submit that this is very helpful in
18 addressing the issue of whether celecoxib is thrombogenic.

19 Question?

20 DR. M. WOLFE: There is still a question I do
21 have. I am not sure if it is answerable, that the pooled
22 data had a lot of patients on aspirin.

23 The real issue to me is when you take people who
24 are predisposed to having thrombotic events, people with a
25 prior history of MI, who really should not be at least

1 theoretically on a COX-2 inhibitor by itself, do you have
2 data to show that those who had a previous history of
3 thrombotic events, who were treated with celecoxib only,
4 without aspirin, did not have an increased risk? I hope you
5 understand the question.

6 DR. FAICH: Well, I think I did. You are asking
7 me are patients who should be on aspirin, but weren't, and
8 if they are on celecoxib, what is their experience?

9 DR. M. WOLFE: That is right. They should be on
10 aspirin.

11 DR. FAICH: I think I might turn that back to Jim
12 Lefkowitz. The answer is the numbers get very small. There
13 are about, if I remember correct, Jim, about 800 such
14 patients in the trial, but we have no power at that point
15 once you start looking at those patients. There is no
16 signal there.

17 DR. M. WOLFE: That is right. The power is not
18 there to exclude the possibility. You have protected those
19 patients appropriately by putting them on aspirin.

20 DR. FAICH: I indirectly can give you one other
21 bit of information. You know in this pooled analysis that I
22 just showed you, as patients rolled out of the control
23 trials onto open-label celecoxib, there was an opportunity
24 to look at the question of when patients switch from a
25 nonsteroidal to celecoxib alone, do they "lose protection"

1 and was there some pattern of elevated numbers of events,
2 and there weren't. When we look at that time course, it was
3 perfectly level, so that we didn't see a bump up in cases.

4 That doesn't quite address that, but those
5 patients were commingled.

6 DR. GEIS: We have a slide that will show you the
7 data that I believe you asked for, so if Dr. Lefkowitz can
8 show that.

9 DR. LEFKOWITH: Because within the CLASS trial we
10 were able to collect all this information prospectively, we
11 at least have some data to speak to that specific issue.

12 Can I have the slide, please.

13 [Slide.]

14 Again this is the rate of MI or stroke in patients
15 who had an indication for secondary prophylaxis using the
16 FDA guidelines. The population in the trial was
17 approximately 150 patients in both the celecoxib and NSAID
18 treatment arms. There were two infarcts in the celecoxib
19 group, one in the NSAID group, for rates that were not
20 significantly different from one another, and no strokes in
21 the celecoxib patients and three in the NSAID patients.
22 Again, those rates are not different than one another.

23 DR. M. WOLFE: Clearly, the numbers are too small
24 to say anything. The reason I am raising this question is
25 because no patient should be under the impression that these

1 drugs would be cardioprotective. I know you don't think
2 that, but they may think that.

3 DR. GEIS: We have never taken that position that
4 they are.

5 DR. HARRIS: Thank you very much.

6 Does that conclude your remarks?

7 DR. GEIS: Yes, it does. Thank you.

8 DR. HARRIS: Thank you.

9 There is another question. Dr. Harrell.

10 DR. HARRELL: We keep hearing the phrase thrown
11 around "something wasn't statistically significant" or
12 "something wasn't powered to even look at what we are
13 looking at," and I think what we are not getting in the
14 presentation is confidence intervals for the relative risks
15 and for the risk differences, and we really need to base
16 what we are talking about right now on those confidence
17 intervals.

18 DR. HARRIS: Brief response if possible?

19 DR. GEIS: Dr. Faich will respond.

20 DR. FAICH: I take your point, and I think you are
21 right. What I was trying to say on that last pooled
22 analysis where the rate was 9 per 1,000, when we did power
23 calculations on that, we can say with confidence that the
24 true number is between--and we did it as a two-tail--and, of
25 course, that is a retrospective pooled analysis, so I

1 understand that, but the true number is going to be between
2 7 and 11. That is what I was trying to say. That is the 95
3 percent confidence limits around that 9.1 number.

4 DR. HARRELL: I don't think you want to be talking
5 about power once a study is done, and if you could just
6 separate those two things and just give us the real
7 confidence limits for the relative risk of the two columns
8 and for the risk difference, because you really need to
9 think about absolute harm or benefit. That would be much
10 more helpful than what we saw there.

11 DR. HARRIS: Go ahead.

12 DR. GEIS: So, we do not have the relative risks
13 at this point. We can try to calculate those and bring
14 those forward later on.

15 DR. SAMPSON: I was wondering if the sponsor had
16 the data on patient disposition and adverse events broken
17 out by the two studies that was discussed earlier this
18 morning?

19 DR. GEIS: Yes, we do have that data. Dr.
20 Lefkowitz can present those data now.

21 DR. LEFKOWITH: Could I have the slide, please.

22 [Slide.]

23 These are the numbers that you asked for, for
24 Protocol 035, in terms of disposition. Approximately 37
25 percent of the patients completed the study in the celecoxib

1 arm, 35 percent in the ibuprofen arm.

2 Withdrawal rates are shown here, as well as the
3 withdrawal for adverse event, treatment failure, which was
4 significantly higher in ibuprofen even within the study,
5 other reasons, and again no lost to follow up patients.

6 [Slide.]

7 More patients completed Study 102, but the studies
8 were staggered and start, so 035 began slightly before 102,

9 so that difference is simply attributable to the fact that
10 they were not precisely contemporaneous. Withdrawal rates
11 are shown. Adverse events again were significantly more
12 common in the diclofenac group. The other withdrawal
13 reasons are shown, again no loss to follow ups.

14 Did you want adverse events, too? Okay. Could I
15 have the next slide, please.

16 [Slide.]

17 As shown within the context of this one separate
18 protocol, adverse events are shown here in terms of those
19 causing withdrawal. Celecoxib and ibuprofen were comparable
20 in that regard as I showed you for the entire study.

21 [Slide.]

22 Within the context of Study 102, there were
23 significantly more withdrawals in diclofenac relative to
24 celecoxib, and again that difference was driven by
25 withdrawals for GI adverse events or hepatic adverse event.

1 DR. HARRIS: First, Dr. Sampson, are you
2 satisfied?

3 DR. SAMPSON: Yes, that's fine. I wanted to see
4 particularly the diclofenac versus Celebrex study, the
5 withdrawal rates and the adverse event rates for that.
6 Thank you.

7 DR. HARRIS: Dr. Cryor.

8 DR. CRYOR: Just in follow up to those slides that
9 you just showed, could you go back to the first two that you
10 showed, because I think it conflicts a little bit with my
11 understanding of the completers of the study from what you
12 showed us earlier this morning.

13 The issue really is in the second slide there, it
14 appeared that the percent of diclofenac group that completed
15 the study was actually less than the celecoxib group,
16 however, earlier this morning, if I remember correctly, the
17 treatment arm that had the highest completion rate was, in
18 fact, the diclofenac group.

19 DR. GEIS: We can explain that, Dr. Lefkowitz.

20 DR. LEFKOWITH: I think we should start from the
21 fact that this was one study. Even though it is conducted
22 as two separate protocols of reasons of blinding, it is
23 really one study and was prospectively designed to be one
24 study and be analyzed as one study.

25 So, I think in looking at the component protocols,

1 one can be drawn to comparisons that are misleading because
2 the protocols were not performed precisely
3 contemporaneously.

4 So, in terms of overall withdrawals, patients
5 completing the study were those who were present in the
6 study when it terminated, when the entire study was
7 concluded, and certain patients also who were participating
8 in Study 035 actually reached a 52-week period before the
9 study was extended by amendment.

10 So, looking at the individual protocols is a bit
11 misleading. Now, if you specifically want to look at
12 diclofenac versus celecoxib, I think the least misleading
13 way or the best way to look at it is actually to look at the
14 entire study as a whole, but I am willing to review it in
15 any way you would like.

16 DR. CRYOR: There just appeared to be a difference
17 with respect to looking at the overall combined study
18 analysis versus the individual protocol. That was the only
19 point I wanted to raise for clarification.

20 DR. HARRIS: There was one other question.

21 DR. NISSEN: I just want to do a quick reality
22 check to make sure that I have the numbers right. But in
23 reading from the FDA's briefing document, in the overall
24 group, the way we have it here is there were 19 myocardial
25 infarctions in the celecoxib group, 4 in the diclofenac

1 group, and 9 in the ibuprofen group.

2 Are those numbers correct?

3 DR. GEIS: We would have to pull up the slide and
4 just confirm that.

5 DR. NISSEN: Okay. And then the other is unstable
6 angina. There were 8 in the celecoxib group, 4 in the
7 diclofenac group, and zero in the ibuprofen group.

8 I just want to make sure I have the numbers
9 correctly.

10 DR. GEIS: We can speak to that issue quickly.

11 DR. LEFKOWITH: I think again if you simply add
12 categories of adverse events, you can be drawn to the wrong
13 conclusion because these events are not simply additive.
14 Patients are coded according to the events they present, and
15 they can be multiply counted, so that you need to do an
16 exclusive listing, that is, to count each patient once and
17 only once.

18 In the analysis that Dr. Faich showed you, that
19 kind of accounting was taken care of, so you cannot simply
20 add those numbers up in the fashion that you are suggesting.

21 DR. NISSEN: Is that right from the FDA's
22 perspective?

23 DR. WITTER: Say the numbers again.

24 DR. NISSEN: Nineteen MI's in the celecoxib group,
25 4 in the diclofenac group, and 9 in the ibuprofen group, and

1 are those different events from the 8 unstable angina in the
2 celecoxib, 4 in the diclofenac, and the zero in the
3 ibuprofen? In other words, are those unique events or not?

4 The reason I am asking that is that in the public
5 discussion question, the question was raised is there an
6 excess rate of adverse serious thrombotic events, and I am
7 trying to get a sense for those absolute numerical
8 differences.

9 DR. WITTER: I am looking at my review, too.

10 DR. LEFKOWITH: We will have to check specifically
11 the numbers. I believe the numbers in the FDA briefing
12 document, as I recollect them, are correct, but you must
13 recall there is a 2 to 1 randomization.

14 DR. NISSEN: I understand that.

15 DR. LEFKOWITH: You simply can't compare the
16 numbers without noting the fact that they have different
17 denominators.

18 DR. NISSEN: Oh, I understand that completely. I
19 just want to make sure I have got the raw numbers right. I
20 can calculate the event rates. What I am trying to get at
21 here is some weighing of the risk and benefit here of the
22 drug, and obviously, there is some differences in GI events,
23 and there is some differences in cardiac events, and I am
24 trying to get a very clean look at that balance, and so that
25 is why we need to know what these numbers really are.

1 DR. WITTER: I have it broken up here into aspirin
2 users and non-users, so I guess we combine it.

3 For celecoxib 19 events. For diclofenac 5 events.
4 For ibuprofen 9 events. This is for MI. Were those the
5 numbers you were referring to?

6 DR. NISSEN: Yes. Those are unique events then,
7 they are not double counting?

8 DR. WITTER: Right.

9 DR. NISSEN: Okay.

10 DR. WILLIAMS: Those seem to be different numbers
11 than were just given to us. Could you give us your number
12 again from the sponsor?

13 DR. LEFKOWITH: Sure. Again, before giving the
14 numbers, we may be talking a little bit about different
15 types of events. The FDA briefing document I believe refers
16 to serious adverse events, and what Dr. Faich referred to
17 was adverse events, and both numbers sound correct, we shall
18 check them, but we should define what we are talking about
19 and we can provide the comparison you want.

20 DR. WILLIAMS: I think we would all agree that
21 MI's are serious events.

22 DR. LEFKOWITH: Not by the technical regulatory
23 definition, no, sir.

24 DR. WITTER: Let me take off on that point
25 actually. I mean, when these are reported--I am looking at

1 Table 54 and 55 of my review, for example, which for the
2 most part comes from Dr. Throckmorton's review, but also
3 obviously from the original database, and I might point out
4 that I don't have any disagreements as far as I am aware
5 except for some of the counting of some of the deaths in
6 looking at attribution for greater than or less than 28
7 days, which doesn't change any of the assumptions.

8 All the data I have looked at, obviously
9 exhaustively, as have others, and I don't think there is any
10 disagreement between the numbers. It may be some confusion,
11 as was pointed out, in terms of how we are looking at it,
12 for example, as a percent or patient years, was reported as
13 an adverse event or as a serious adverse event.

14 The numbers I just read to you were for adverse
15 events. If I looked to serious adverse events and combined
16 them, I think it is essentially the same. It is 19 for
17 celecoxib, it is 4 for diclofenac, and it is 9 for
18 ibuprofen. I think I said 5 before for diclofenac.

19 DR. NISSEN: Those correspond to the data that I
20 am using in analyzing this, but it is confusing to us
21 because there is a lot of different numbers being thrown
22 out, and if you really want to calculate an absolute risk
23 versus absolute benefit, you have got to have some sense of
24 what those real rates are.

25 DR. WITTER: And this is what we are hoping is

1 part of the discussion here, to help us clarify how to look
2 at this data, as well.

3 DR. WOFYSY: I don't know whether anyone is needed
4 on this point, but it seems to me that whichever numbers we
5 look at, we are talking about roughly a 30 percent
6 difference between the celecoxib group and the other groups
7 in an area which is very small numbers.

8 Even the comparison on MI's that you have listed
9 as 0.5 and 0.4, it is actually 0.54 and 0.37 when you
10 calculate it out, so it, too, comes out to be about a 25 to
11 30 percent difference. But it is a 25 to 30 percent
12 difference in numbers that are so small that they don't
13 approach statistical significance, and I think that is the
14 challenge which of course has been put forward clearly by
15 the sponsors who understand this, too, that we are dealing
16 in numbers too small to achieve statistical significance,
17 and we are dealing in differences between the groups that
18 could conceivably be meaningful enough to be important.

19 DR. GEIS: Could we comment, Dr. Faich, who has
20 reviewed these data for us, if he could make a comment?

21 DR. FAICH: It is a simple comment. I mean when
22 you have small numbers, you try to go to a bigger data set.
23 That is why I went to the pooled data, because you have more
24 confidence in the numbers. There, you are looking at 90, as
25 you recall, versus 23, and that was in the nonsteroidal arm,

1 which had roughly a third of the exposure, a little less
2 than that, and there you saw virtually no difference.

3 That is why that was done, at least that is why I
4 did it, because I looked at that and I said, yes, small
5 differences, and is there a trend there or isn't there a
6 trend there, and that is the very reason you go to a larger
7 data set.

8 That larger data set, I might say, had all of the
9 elements of complete capture of patient follow up, we knew
10 about their exposure. That is why it made sense to pool
11 them. So, at least again, as I said before, that is the
12 most robust thing you can look at, and there is no
13 difference.

14 DR. HARRIS: I think we have been satisfied. Is
15 there one more comment that you would like to make?

16 DR. GEIS: No, we have satisfied all our comments
17 at this point. Thank you.

18 DR. HARRIS: Thank you very much. Dr. DeLap.

19 DR. DeLAP: I would like to weigh in with one
20 brief comment on this topic. I think we are very concerned
21 about cardiovascular events as something that it reflects an
22 illness that is common in our population, and we want to be
23 sure we understand what effect we might or might not be
24 having, and we have put a lot of thought into this.

25 One of the issues that we have that has not been

1 mentioned with the kind of combined or larger analyses,
2 pulling in additional databases, is just that inherently,
3 other studies are done in different patient populations and
4 different eligibility criteria often and different durations
5 of studies, and so we draw some security from those kinds of
6 analyses, but it is not just a bigger data set that is
7 telling you the same thing as what the smaller data set, it
8 is another way of looking at some more data, which again it
9 is more reassuring not to see something than see something,
10 but it is not an answer if you don't see something.

11 DR. HARRIS: Thank you. I think we have probably
12 expanded that some more as the discussion goes on this
13 afternoon with some of the questions.

14 **Discussion and Questions**

15 DR. HARRIS: I think you all have the questions
16 before you, and I want to start with the first question,
17 which was posed to us by the FDA.

18 The question reads: Has a clinically meaningful
19 safety advantage been established for Celebrex compared to
20 ibuprofen and/or diclofenac? Please respond specifically
21 for upper GI safety and separately for global safety.

22 Now I thought we might move forward with this is
23 we will start with upper GI safety. Let's go around the
24 room and discuss that. Perhaps, I thought that one of the
25 issues, of course, is what is a clinically meaningful safety

1 advantage, does it mean the same thing to all of us with
2 respect to upper GI safety, and to get the ball moving, I
3 thought that I would ask Dr. Cryor perhaps to comment.

4 DR. CRYOR: I would be happy to comment. With
5 regard to my comments, I don't have the eloquently written
6 out comments that Dr. Sidney Wolfe previously had, but I do
7 have a few thoughts on the issue, but I think that you
8 precisely stated the issue with respect to a clinically

9 meaningful safety advantage, and it really depends from a
10 gastrointestinal perspective on how we are going to define
11 it.

12 There has been a lot of discussion this morning
13 with respect to whether we give higher priority to
14 symptomatic ulceration or to complications of ulceration.
15 Where you fall on this issue is going to really determine
16 the answer, I think.

17 Based upon the data that we have seen this morning
18 from both the sponsor, as well as the agency--which, by the
19 way, I thought all presentations were exceptional--looking
20 at the overall group of individuals from the CLASS trial, if
21 you look at the sponsor's primary endpoint, complicated
22 ulceration, and I guess the question is being asked
23 specifically in comparison to diclofenac and then to
24 ibuprofen, for the overall group for primary endpoint
25 complicated ulceration, no difference from either, but with

1 respect to the composite including symptomatic ulceration,
2 again, we have divergent results, diclofenac, ibuprofen,
3 there appear to have been a difference.

4 I think the more clinically relevant question with
5 respect to biologic effects of celecoxib not confounded by
6 another agent such as aspirin is to look at the non-aspirin
7 group, and again, just going through the similar analysis,
8 we saw today that again, if you look at primary endpoint of
9 complicated ulceration for diclofenac, no, there appeared to
10 be no clinically meaningful safety advantage, but with
11 ibuprofen, yes, and the same for the secondary consideration
12 of composite ulcerations which included the symptoms.

13 One of the questions that I asked earlier, and I
14 am still not entirely clear as to the answer, is again this
15 confounding effect, because what I am trying to get to, I
16 think what we are trying to get to in Question No. 1 is
17 specifically for celecoxib, what is the potential clinical
18 safety advantage.

19 So, we have removed in part of our assessments the
20 confounding effect of low dose aspirin, but it would be
21 helpful to also remove the potential confounding effect of
22 OTC NSAIDs. Prior to today, I was not aware of the
23 percentage of the population in the study that was taking
24 OTC NSAIDs, but I think it is significant enough that it may
25 potentially have impact if you think about the 21 percent of

1 individuals who potentially had a confounding association of
2 aspirin plus the 5 to 6 percent, let's say 6 percent on OTC
3 NSAIDs, that's 27 percent of the population that is
4 potentially confounded, and so what I think would be helpful
5 into getting the answer to Question 1 would be to look at
6 the 73 percent who were not on OTC NSAIDs and not on low
7 dose aspirin with respect to the different endpoints.

8 In prioritizing each of these endpoints,
9 symptomatic ulceration versus complicated ulcers, I do, in
10 fact, think clinically that symptomatic ulceration is a
11 clinically meaningful endpoint and a clinically important
12 endpoint, and this is one of the arguments that the sponsors
13 have been bringing forth this morning.

14 I think it is important with respect to patient
15 referrals for endoscopic procedures based on dyspepsia with
16 respect to health economics, with respect to consumer
17 satisfaction, but with respect to prioritizing each of the
18 endpoints, and making them in the background of morbidity, I
19 am going to have to say that complicated ulceration takes a
20 greater priority and is likely the more clinically
21 meaningful endpoint with respect to assessing a safety
22 advantage of celecoxib.

23 So, with respect to the endpoint of, in my
24 opinion, of highest priority, the complicated ulceration, it
25 didn't appear to differentiate from either diclofenac or

1 ibuprofen.

2 There has also been this argument, this discussion
3 point raised by the sponsors this morning that the reason
4 that we are not seeing these differences between diclofenac
5 group and the celecoxib groups is with regard to there being
6 a lower than expected incidence rate of events in the
7 diclofenac group.

8 That is why I recently asked the question about

9 what the actual percent completion rate in the diclofenac
10 group might have been. I think this is important because I
11 think the sponsors propose the argument that the increased
12 withdrawals in the diclofenac group were secondary to
13 gastrointestinal adverse events, and for that reason,
14 because these people in the diclofenac arm weren't allowed
15 to have persistent exposure to diclofenac, they then didn't
16 go on to develop those complications.

17 But then later this morning Dr. Witter, I think,
18 pointed out that some of those gastrointestinal withdrawals
19 were, in fact, related to liver function, liver test
20 abnormalities, and not specifically gastrointestinal,
21 complications or adverse events such as dyspepsia, but
22 nevertheless, I am not entirely clear as to what the reasons
23 for the withdrawals are.

24 I think there are two points that I want to make
25 about the diclofenac comparison. Discontinuation in the

1 diclofenac arm irrespective of the ultimate explanation in
2 and of itself might be protective from the development of an
3 event, so if we have patients who stop diclofenac early
4 because they are having symptoms, that, in fact, reduces the
5 event rate and may be to some degree protective.

6 Also, as I stated earlier, the sponsors state in
7 their Slide No. 93, with respect to patient disposition,
8 looking at completers of the study, that the highest

9 completion rate on a percentage basis was, in fact, in the
10 diclofenac group.

11 I also think that how we defined clinically
12 meaningful safety advantage also has to be considered with
13 respect to time. If we think back to the time courses that
14 we saw over one year between celecoxib and NSAID
15 comparators, one of the observations that I made on the
16 slides earlier was that, in the short term, it appeared that
17 in the first 90 days, there was no separation between the
18 curves, between NSAIDs and celecoxib or specifically
19 ibuprofen and celecoxib. We weren't shown the curves
20 comparing time analysis of diclofenac versus celecoxib, but
21 nevertheless, given the overall lack of difference between
22 the NSAID group combined, I think there probably wouldn't
23 have been a difference.

24 So, in the short term, there didn't appear to be a
25 clinically meaningful safety advantage with respect to the

1 time curves, however, if you look at a year, there was a
2 clinically meaningful safety advantage, so again, it is
3 qualified depending on duration of exposure and time course.

4 One of the other qualified responses that I have
5 with respect to how we are going to characterize this, an
6 aspect that has actually been underemphasized is this
7 significant reduction in hemoglobin and hematocrit over time
8 that was seen with celecoxib compared to NSAID comparators.

9 Although these aren't complicated ulcers or symptomatic
10 ulcers, this, nevertheless, is a very clinically important
11 outcome, deleterious consequence of NSAID use which drives
12 again, as I suggested earlier, a lot of diagnostic
13 evaluations for hemoccult-positive stools and evaluation of
14 anemia, and also may complicate because of the presence of
15 anemia the comorbid diseases.

16 So, I think I would suggest to the committee that
17 you might also want to consider whether or not this dramatic
18 reduction in hemoglobin and hematocrit loss is a clinically
19 significant event.

20 The next qualified comment with respect to how we
21 are going to define clinically meaningful safety advantage
22 comes down to a risk group analysis. The individuals who
23 may be in some people's minds preferred candidates for COX-2
24 specific inhibitors or specifically celecoxib, if you look
25 at the oldest age group, age greater than 75, comparing

1 celecoxib to the NSAIDs, there were no differences, they
2 were similar, so in that age group it appeared to be no
3 clinically meaningful safety advantage.

4 With regard to those who have a history of upper
5 GI bleeds, yes, there is a reduction associated with
6 celecoxib, but then in a very important group of those who
7 are the combination of celecoxib and low doses of aspirin,
8 in fact, it appears very interestingly that there might be

9 actually an increased event rate in those who were taking
10 the celecoxib and aspirin.

11 So, just to summarize what I have said over the
12 last several minutes, how we answer this question with
13 respect to is there a clinically meaningful safety
14 advantage, really is qualified, and it depends on which
15 variables we look at.

16 It seems to be based upon which NSAID it is being
17 compared to, their differences. Our answer is going to be
18 different if we make the comparison with ibuprofen versus
19 diclofenac. It is going to depend importantly, very
20 importantly on whether there is concomitant aspirin use or
21 not.

22 The time course is important, are we making this
23 analysis in the short term, in the first 90 days, or in the
24 long term, and what are the risk groups' characteristics,
25 and then finally, I think we need to consider this in light

1 of the hemoglobin and hematocrit decline, which I think
2 actually is something that is important for you to consider,
3 as well.

4 DR. HARRIS: That you for that comprehensive
5 review, Dr. Cryor. That, indeed, is the heart of the
6 problem that we face with clinically significant events, and
7 really, I am going to ask for more comment, but let me start
8 by asking this.

9 Is any one of the various items arise as being
10 clinically significant, or do we have to have all? For
11 instance, as was pointed out, if it was a clinically
12 significant ulcer event, would that alone be sufficient to
13 say that it is clinically meaningful, or do we need, in
14 fact, to have the combined events?

15 In other words, what I think we need to be saying
16 is in terms of clinically meaningful, is there any one
17 single group that would enable us to say that this is a
18 clinically meaningful difference, or do we, in fact, have to
19 put all the various qualifiers in to say that this is going
20 to be a clinically meaningful difference?

21 I don't know if anybody might want to comment.

22 DR. M. WOLFE: I will be a little briefer. These
23 are very difficult studies, first of all, because if you
24 look at most people with abdominal pain and dyspeptic
25 symptoms, most don't have ulcers. If you look at people

1 with ulcers, most don't have symptoms.

2 So, for that reason, I agree with Byron, that the
3 most objective parameter to really assess is what has been
4 referred to as PUBs, the complicated ulcers, because those
5 are indisputable, someone has a perforation or a bleed due
6 to an ulcer, we know that is a clinically significant event.
7 If someone has abdominal pain due to an ulcer, that person
8 doesn't care if they have an ulcer or not, they are in pain
9 whether they have an ulcer or not, so that is dyspepsia with
10 or without an ulcer.

11 So, the question that is being asked here, have we
12 really established, has the sponsor established clinically
13 meaningful data which will allow us to conclude that there
14 is a distinct safety advantage.

15 We heard two very different presentations today
16 based on the data with very different analyses, very
17 different conclusions. The onus of proof is on the sponsor
18 to show that they are indeed different from the other
19 agents.

20 After looking at the data presented, I can come to
21 the conclusion that I can't conclude that at the present
22 time, so I would have to say at the present time, from what
23 I have seen, the upper GI toxicity we are talking about--and
24 that is a question to ask--upper GI safety appears to be
25 similar to those, to at least again to the different

1 presentations, I cannot say that it is different from the
2 standard NSAIDs.

3 DR. WILLIAMS: I have just a little different
4 interpretation on that. My conclusion would have been that
5 I did think they showed a clinically meaningful and
6 statistically difference from ibuprofen, but not from
7 diclofenac, but these differences cancel out if they take
8 aspirin at the same time, so that in the absence of aspirin,
9 they do show a difference with one of the two NSAIDs, but
10 not with the other, so I am not sure what that means in the
11 totality of things.

12 I think they did show they were different than
13 ibuprofen, but if you take aspirin on top of that, you can't
14 cite any benefit.

15 DR. M. WOLFE: Again, the sponsors have said this
16 is one study with two comparator NSAIDs. Therefore, putting
17 the data together, I can't come up with a difference.

18 DR. WILLIAMS: I agree if you are going to combine
19 both NSAID comparators together, you didn't see a
20 difference, but I think if you look at the fact they had two
21 comparators, they did show it with one, but not with the
22 other.

23 DR. CRYOR: I think in trying to generalize this
24 to a clinical population is we are not going to be able to
25 predict which NSAID comparators patients are going to be on

1 in clinical practice, and if, in practice, there was
2 exclusive use of diclofenac or ibuprofen, then, we would be
3 able to more specifically state with certainty yes or no,
4 and I would agree with you, but we can't, because we have a
5 continuum of event rates with the nonselective NSAIDs.

6 DR. WILLIAMS: I perfectly agree with you, Byron.
7 I think that the fact that they didn't show it with both
8 means you can't make any generalizable statements.

9 DR. HARRIS: Just out of interest, suppose they
10 did show it was both, could one have generalized?

11 DR. CRYOR: On the basis of the study as proposed
12 and designed, the answer would be yes, however, then I also
13 want to reiterate a point that I just made, that we have
14 this continuum of NSAID toxicity associated with the
15 nonselective NSAIDs, and in general, based upon the
16 cumulated experience of the studies, it appears that
17 diclofenac and ibuprofen fall on the lower end of that
18 spectrum.

19 So, if you are showing a difference between the
20 ones that fall on the lowest end, you would expect that you
21 would find there is clearly a difference with the ones that
22 were more toxic.

23 DR. ELASHOFF: Janet Elashoff. It is certainly
24 clear that no difference has been shown for the complicated
25 ulcer. There have been some arguments that we ought to pay

1 attention to differences that might or might not have been
2 shown when you add in symptomatic ulcer, and from some
3 points of view, that seems reasonable, although as soon as
4 one gets there, it seems to me that if there is to be a
5 clinically meaningful safety advantage on some front, it
6 ought to be showing up in the overall rates because if you
7 have substituted some other safety problem for a safety
8 advantage, I don't see any benefit of sort of advertising a
9 safety advantage.

10 If you look at overall serious adverse events,
11 although certainly not statistically significant, it is
12 higher in the celecoxib group than in the others, so that
13 even should one be paying attention to the symptomatic part,
14 it doesn't translate into an overall advantage even
15 numerically that we can see, but there is a numerical
16 disadvantage.

17 So, I think that if one is talking about an
18 advantage, it ought to show up clear through all adverse
19 events, and not just when we look at some specific category
20 of adverse event.

21 DR. NISSEN: Well, you said very well what I had
22 wanted to say, and that is, to a patient, it doesn't matter
23 what the serious adverse event is. Whether you have a
24 myocardial infarction or get admitted to an ICU with a
25 bleeding ulcer, to a patient, I am not sure you would pick

1 one over the other, and so when I looked at all of these
2 data, I asked a simple question - among the serious
3 complications that may or may not be associated with these
4 agents, was there an overall advantage, and I just did the
5 same math you did, and what I got was for death, MI,
6 unstable angina, or a complicated ulcer, 58 events in the
7 celecoxib group and 52 events in the comparator groups.

8 So, among the really potentially life-threatening
9 or very serious complications, including death, there
10 certainly is no difference and no advantage whatsoever, and
11 so it is hard for me to make the GI safety determination out
12 of the context of the overall benefit for the patient, which
13 I just don't think has been shown here in the trial all the
14 power calculations notwithstanding.

15 DR. PINA: I think Dr. Cryor put it very
16 eloquently, my analysis of things. I am also very struck by
17 the withdrawal numbers, and the withdrawal numbers in all
18 the groups are rather high, which tells me that the
19 population that completed the study may have been
20 subselected by itself because of less adverse events, and
21 this happens in a lot of large trials where you have
22 difficult patients with multiple comorbidities.

23 I am also concerned that the age group that this
24 is being used in is, in fact, the age group with the highest
25 cardiovascular mortality - women, postmenopausal, where

1 heart disease is the number one killer, and if you are going
2 to start to think about aspirin added to whatever else they
3 are on, I am coming to that in a minute, I don't see a
4 dramatic advantage to this at all, I don't see an advantage
5 to this at all.

6 I have not heard anything about concomitant
7 medicines, and that has got to be put into the equation
8 because these are, in fact, the people with the comorbidity,

9 so I think that the population was very selected, and the
10 population selected itself as the trial was going on because
11 of the large number of withdrawals.

12 DR. HARRIS: Perhaps I can pose this question to
13 the rheumatologists at the table because invariably, when we
14 are using nonsteroidals, I think one of our big concerns is
15 GI toxicities. The issue whether or not based on the data
16 that we have heard today, whether or not one would feel that
17 there is a distinct advantage there, something that we can
18 tell our patients about Celebrex with respect to significant
19 GI complications. Suppose I were to raise that.

20 Would we recommend it surely before we do any of
21 the other nonsteroidals?

22 DR. WILLIAMS: I am a rheumatologist, so I will
23 answer. The think that the data today is confused based on
24 other data I have seen in the past because I was convinced
25 that this was safer, that the COX-2 inhibitors were safer.

1 I think the data doesn't necessarily show that
2 today except I think there is an exception. I think as
3 aspirin cancels out any benefits you expect to receive from
4 specific COX-2 inhibition.

5 Now, the data did give me some hope in terms of
6 ibuprofen, but I felt that the fact that we weren't able to
7 show differences in diclofenac makes this so I can't
8 generalize that in discussing it with all nonsteroidal anti-
9 inflammatory drugs. Based on the data seen today, I can
10 only tell them that versus ibuprofen.

11 DR. WOFYSY: Dave Wofsy, also a rheumatologist from
12 UC/San Francisco.

13 The challenge here for me is that it seems to me
14 everybody is speaking truth. I agree with everyone who
15 speaks. I agree with the sponsor and their emphasis, I
16 agree with the FDA in their description, and I agree with
17 everybody around the table who has spoken.

18 I think that is the dilemma here. It depends on
19 which piece of this you pick out. So, let me simply say why
20 I think that that is all so and how it translates into
21 people with rheumatic diseases.

22 The primary endpoint wasn't met, it wasn't close
23 to being met, so that is truth. The attempt to show that
24 this is safer required retrospective redefinition of what
25 the endpoints were and what the groups were, and that is

1 certainly less than compelling.

2 On the other hand, I do believe that the arguments
3 that were made based on those retrospective analyses are
4 very interesting and seriously point to the possibility, as
5 Jim Williams has said, that in people who aren't taking
6 aspirin and perhaps for certain nonsteroidal anti-
7 inflammatory drugs, this is a safer approach with respect to
8 GI toxicity.

9 I think that is strongly suggestive, not proven,
10 and I don't think anybody here could really claim that it is
11 proven given the manipulations, but I can't discount it.

12 I would also like to underscore two other things
13 that were said by others that relate to this. The lack of
14 any difference at all between the groups in overall serious
15 safety problems, it seems to me to be a very important
16 point. However you want to juggle these data, the patients
17 in one group were no more or less likely to have something
18 bad happen to them than the patients in the other group. I
19 think I agree very strongly with the point that from the
20 patient's point of view, that is key.

21 I also think it underscores a dilemma. The
22 biggest dilemma for the sponsor, I don't know what to do
23 with this, you have come forward with data that say, that
24 strongly suggest to me that celecoxib has a GI advantage
25 compared to one NSAID, but not compared to another.

1 Well, there are 10 NSAIDs out there. If we did
2 them all, and I promise you I am not suggesting that the FDA
3 require you to do this, but if we did them all, would we
4 find that you were better than nine, and not better than
5 one, or would we find that you were better than one, and not
6 better than nine, or where does it fall in between?

7 So, there are all these kinds of questions that
8 come up in this where I must say one is left to decide which
9 truth is most important to them, and ultimately, I suppose
10 the way that works is that the truths be laid out for the
11 patients, and the patients get to decide that.

12 DR. M. WOLFE: As a gastroenterologist, I feel
13 compelled to--and studying ulcers the last 20 years--feel
14 compelled to make a comment regarding the endoscopic data,
15 which is so different from what we are seeing here, and
16 there is an explanation, something that was mentioned at the
17 very beginning, and that is that if you look at the point
18 prevalence of ulcers in the population, it is somewhere
19 around 3 to 5 percent depending on the study we look at.

20 So, in other words, there are people in this room
21 with an ulcer right now, you might not even know it, and
22 what does that mean? In an endoscopic study, that person is
23 excluded from the study to start off with. In the real
24 world, that person goes on a drug which blocks COX-2 very
25 effectively.

1 Well, COX-2 is found at the end of the ulcer
2 helping with angiogenesis, helping to heal the ulcer.
3 Therefore, the theoretical concern--and none of these
4 studies answer this question, they haven't been designed to
5 look at it in humans--it is possible then by specifically
6 inhibiting COX-2, you can theoretically make a preexisting
7 ulcer not heal. So, that could be an explanation of the
8 divergent results between the endoscopic studies and an
9 outcome study.

10 DR. WILLIAMS: However, traditional NSAIDs also
11 inhibit COX-2, so that shouldn't be much different, should
12 it?

13 DR. M. WOLFE: That is exactly right, and they
14 weren't different.

15 DR. WITTER: If I could just clarify for a bit,
16 and just give another little spin to this question before we
17 move on, just to review in terms of, for example, deaths, be
18 they for all causes or for cardiovascular causes, no more
19 prevalent in celecoxib.

20 If you look at adverse events overall or as we
21 define mild, moderate, and severe, no more prominent in the
22 celecoxib group. Serious adverse events were more common as
23 we had noted, but that is in association, not necessarily I
24 think one that we say is definitely a causal relationship,
25 but I think as Dr. Goldkind had tried to discuss.

1 Also, when you look at the data, although we talk
2 about trends and such, when you pool, if you look at the
3 analysis in a pooled fashion against the expanded endpoint
4 in those folks not taking aspirin, celecoxib was better than
5 the pooled, and that was being driven obviously by the
6 ibuprofen comparison.

7 The point that I would like to put in, if it is of
8 any use, and I have struggled with this a lot in thinking

9 through this data, celecoxib as we now know was at a super-
10 therapeutic dose, but the comparators were not at that kind
11 of dose, and so I often wonder what the discussion would be
12 had the comparison been twice of the NSAIDs as they
13 represent and twice of this.

14 I just wonder if that factors into any of your
15 thinking or your conclusions.

16 DR. HARRIS: Well, let me raise that issue and
17 raise that last question, which is that, of course, that the
18 celecoxib was at twice the dose.

19 DR. M. WOLFE: Yes, with that dose, if you look at
20 the IC50's at least, looking at the inhibition of COX-2 and
21 COX-1, it is still a selective inhibitor of COX-2 over COX-
22 1. So, it should make a difference at least when we look at
23 IC50's.

24 Again, you raise an important point. All the
25 other traditional ones says there is definitely a dose-

1 dependent response, so we can't answer the question because
2 lower doses weren't examined.

3 DR. GEIS: Dr. Harris, I am wondering if we could
4 contribute to the conversation by responding to some of the
5 comments, because I think we do have some data that can
6 contribute to an understanding of the question and what the
7 data shows?

8 DR. HARRIS: Let me carry the discussion along a
9 bit more here. I think that we have, in fact, heard a lot
10 of clarifications coming from the sponsors, and really, let
11 me hear some more discussion. If there are particular
12 points of clarity that any member of the committee might
13 feel that might be helpful, then perhaps we can ask, but
14 really, this is the time for our committee to do much of the
15 speaking.

16 DR. CRYOR: Dr. Witter, I would like to follow up
17 on the comments from Dr. Wolfe. I see it slightly
18 differently. From a strict scientific study design, the
19 most accurate sorts of endoscopic or safety studies are done
20 at therapeutic dose equivalences, and so even though we
21 wouldn't expect to see significant gastric COX inhibition at
22 that dose of celecoxib, there may, and there probably is,
23 gastric injury that is related to other mechanisms, topical
24 injury, and so because of these other mechanisms, it
25 probably in your discussions would be helpful to consider

1 therapeutic dose equivalences.

2 Having said that, the ultimate argument which won
3 me over with respect to validating the dose of celecoxib
4 that was currently used in the current study is this issue
5 that has been observed clinically of dose creep and the
6 issue of that being a dose that may be used for some
7 indication, such as FAP.

8 DR. PINA: We have heard a lot about the side
9 effect and the complications, and kind of putting on my
10 rheumatologic hat for a moment, which I don't really own,
11 it's yours, the patients come to us with pain, and they come
12 to you with pain. They come to me with shortness of breath,
13 but then they tell me they are hurting, and I have to choose
14 an agent.

15 Did this agent show such benefits in pain
16 reduction when compared to the others, and I think not, so
17 am I willing to take the extra risk if the pain relief is
18 going to be the same? These patients' quality of life is
19 also a big issue at stake here, and you have pointed that
20 out to us - their mobility, their ability to do their ADL's,
21 and had this drug offered a significant benefit in pain
22 reduction, in mobility improvement, and quality of life
23 improvement, then I might say, well, presenting the patient
24 with all the information that there may be risks even if
25 they are on aspirin, they may wish to take it if they feel

1 better, but I haven't heard that for this drug.

2 DR. HARRIS: What I think I will do now, because I
3 just wanted to just ascertain where we are, and in terms of
4 a consensus--yes?

5 DR. WILLIAMS: I just wanted to address Dr.
6 Witter's suggestion, and while the usual dose for rheumatoid
7 arthritis would be 400 mg a day, this drug is certainly used
8 at 800 mg a day, and so I was not particularly distressed by
9 that. The biggest thing that keeps people for using that
10 dose is the cost right now because it is not marketed at
11 that dose, but we know that there are a few people who
12 respond to higher doses, so that there are rheumatologists
13 who use 800 mg--the most common dose would be 400 mg--but it
14 is being used at the higher dose.

15 DR. HARRIS: And, Dr. Witter, I really wanted to
16 emphasize this endpoint, because, of course, the dosage
17 creep is one that arises over and over again.

18 DR. WITTER: In the clinic, are we using
19 diclofenac at--what would it be--300 mg? I am still looking
20 for a little discussion on that issue.

21 DR. WILLIAMS: I can't speak for every
22 rheumatologist, but as I have talked to rheumatologists, I
23 think diclofenac would be pushed occasionally to 225 mg a
24 day, and that occasionally in naproxen goes to 1.5 grams a
25 day. Those would be roughly the frequency in my experience

1 of those who are on 800 of Celebrex.

2 DR. WITTER: Are you more comfortable if you go up
3 to the higher dose of celecoxib versus going up to the
4 higher doses of those that you just mentioned?

5 DR. WILLIAMS: Now, you are getting into real
6 personal opinion, and, yes. I actually would use, if they
7 were tolerating the usual dose and I felt they would do
8 better on a higher dose, any of the three I would be happy
9 to go up on.

10 DR. WOFSY: I think it is fair to say that, I mean
11 inherent in your question, is that Celebrex was put to a
12 harsher test here than diclofenac or ibuprofen, that if you
13 think of the dose ranges we use, certainly one drug in the
14 study was tested at the outer limit of where you would go,
15 and the others were tested in the middle, conceivably even
16 at the low end for certain kinds of indications.

17 But that was sort of a conscious prospective
18 decision that was made, and it would be pure conjecture, I
19 think at this point, to say that the results would have come
20 out any different if the diclofenac had been doubled or if
21 the Celebrex had been halved.

22 I mean clearly these are not comparable on the
23 spectrum of what people use, but it is the only data we have
24 to look at, and I have no strong data that I can cite to
25 suggest that the results would be different if the design

1 had been different.

2 DR. HARRIS: Okay. I think I am getting a sense
3 from the committee, but I will reask the question. I think
4 that there is a consensus which states that there is no
5 clinically meaningful safety advantage of Celebrex with
6 respect to upper GI safety. Supposed I posed it that way.
7 Would one agree with that?

8 DR. WILLIAMS: I would agree with that statement
9 if you are referring to all of other NSAIDs globally. I
10 think you did show a difference for ibuprofen without
11 aspirin, but I think that if you are trying to translate in
12 there to all NSAIDs, no, I would agree with your statement.

13 DR. HARRIS: That is why I framed it that way.
14 So, another comment.

15 DR. SAMPSON: I guess I am even concerned about
16 your statement, Dr. Williams. It is not clear to me even in
17 the non-aspirin users that if you use the primary endpoint,
18 that you have shown a difference between Celebrex and
19 ibuprofen.

20 If you look at the POBs, and there is this 0.037,
21 and the word that I think Dr. Witter and Goldkind used was
22 "trend" for that, and they cautioned, they put other
23 modifiers around it. It is not subject to the multiple
24 comparisons that have been done to get there, that if you
25 did any sort of--it is hard because it's a secondary

1 analysis data driven, but if you do any sort of multiple
2 comparisons procedure, I think you would not arrive at a
3 difference between Celebrex and ibuprofen on the primary
4 variable.

5 DR. WILLIAMS: I would agree with you
6 statistically. I was looking at the clinical
7 meaningfulness, and I thought that cutting the complication
8 rate in half looked pretty convincing to me. I agree that

9 0.037 should be taken with some care because of the multiple
10 comparisons, but I was looking more at the fact that you
11 roughly halve the rate that I felt was relatively
12 impressive.

13 DR. HARRIS: So, you do accept that.

14 DR. HARRELL: You just addressed a piece of what I
15 was going to say, but I think when you go looking at a
16 retrospective analysis and subgroups and different endpoints
17 and all, you want to find a very impressive effect in that
18 group, and we still didn't find that.

19 DR. CRYOR: Personally, I wouldn't state the
20 consensus as emphatically as you did because I think it
21 really depends on who is taking the celecoxib and for how
22 long and with which other medicines, specifically, aspirin.

23 But with respect to the complication of greatest
24 concern, complicated ulceration, I agree, the consensus
25 answer appears to be no.

1 DR. WOFYSY: I would phrase it slightly
2 differently, and then I find it very easy to agree. I have
3 a little hard time saying the answer is no. I have no
4 trouble saying it was not proven, and I think that is
5 clearly true. It was not proven to be safer.

6 There are data here that leave open the
7 possibility that it is safer, safer than all NSAIDs, safer
8 than some NSAIDs. To me, that is an unanswered question,
9 and I would be uncomfortable answering it no.

10 I can say, however, that, yes, wasn't proven.

11 DR. HARRIS: Can I ask one of the statisticians
12 perhaps to just comment about that?

13 DR. SAMPSON: We had a brief discussion of this
14 over lunch. There are lots of suggestive trends in the
15 data. The sponsor has done a very careful analysis looking
16 at other than the primary variables and looking at other
17 risk factors, and I think in terms of our responsibility
18 here is to look at it from a very rigorous point of view,
19 and these other issues that you have addressed, the
20 suggestive results are possibly thoughts that they might use
21 in designing other trials to more rigorously demonstrate that,
22 and to demonstrate in a way that would be both
23 scientifically and statistically and clinically meaningful.

24 DR. NISSEN: I would really like to echo that. I
25 think it is really dangerous for us to make any decisions

1 based upon non-prespecified endpoints, and the problem is
2 once you start to do that, it is a terribly slippery slope,
3 and we have made over the years so many mistakes in doing
4 that.

5 I mean I go over this with our fellows all the
6 time. They come in and they run, you know, 500 T-tests and
7 they come up with a p-value, and they say, ah, it is a very
8 important finding, and I think once you start to split this
9 ~~down into smaller groups and substudies that were never~~
10 prespecified, any conclusions you draw from that are just
11 speculative and are hypothesis generating.

12 Again, given the really large number of people
13 that are going to be exposed to these drugs, our decision,
14 it seems to me, has to be based upon what is appropriate,
15 statistical, you know, analysis, and that is the primary
16 endpoint, and I think the way you stated it for the primary
17 endpoint is correct and has to be seen that way.

18 DR. M. WOLFE: I agree, as you said before, that
19 we have to go with the data that has been presented. On the
20 other hand, you asked us here because of our gut feelings,
21 and the feelings we have, again, we have to give a qualified
22 no. I think that is what we are saying it is a qualified
23 no, we have not proved, it has not been proven that these
24 are safer, but I think we can leave the door open for the
25 possibility that they are in the future, future studies will

1 show that.

2 DR. WOFESY: Since it was my comment, I think to
3 some degree, that drew the disagreement. Let me just
4 emphasize that I agree with the comments that were made
5 following mine. It really is a matter of how you phrase the
6 question. If the question is, as it is here, so I will just
7 read it, "Has a clinically meaningful safety advantage been
8 established for Celebrex," I agree with you the answer is
9 no, and I don't want to hedge on any amount of retrospective
10 manipulation of the data, but if I recall correctly, when
11 the statement was made to the committee, it was made a
12 little differently than has it been established, and the
13 question is, is Celebrex safer, and the answer is no, and to
14 me the answer to that is I don't know.

15 So, I am agreeing, however, with the comments that
16 followed me, that it has not been established. To prove
17 that it is not, as I am sure the statisticians know, is an
18 entirely different study and requires an entirely different
19 set of statistics, and that hasn't been done.

20 So, that is the only point I am saying. We
21 haven't proven that it is not safer. We are convinced that
22 it hasn't been established that it is safer.

23 DR. WILLIAMS: Since Dr. Wofsy wants to agree with
24 everybody, I would like to agree with him. I would soften
25 my answer to say that I like the way he stated it. He