

1 hematocrit or hemoglobin. Hemocult-positive stool and  
2 orthostasis or hemocult-positive stool and the need for  
3 transfusion on clinical grounds.

4 [Slide.]

5 Again, to briefly go through the issues of dose  
6 selection. Again, obviously, the proof of hypothesis was  
7 important to test and to be sure that there wasn't simply a  
8 shallow dose dependency of any GI safety that may be  
9 demonstrated.

10 The dose creep phenomenon has been discussed by  
11 Dr. Witter. Particularly in chronic illnesses, particularly  
12 in painful conditions, a dose creep phenomena is  
13 anticipated, and this would be particularly true if there  
14 was a safety advantage suggested for a particular product,  
15 so that this was again part of the reason for building this  
16 high dose into the design.

17 Again, the margin of overall safety as opposed to  
18 organ-specific safety was important. Obviously, if the  
19 overall safety is not maintained at a higher dose, it is  
20 important to know, so that you can put any organ-specific  
21 safety information into a broader context.

22 Of course, the 8 mg a day dose is the 2X for  
23 rheumatoid arthritis, but it is the 1X for another chronic  
24 condition, familial adenomatous polyposis, and, of course,  
25 the future, we don't know.

1 [Slide.]

2 As the sponsor has pointed out, multiple aspects  
3 of the study address the issue of generalizability in terms  
4 of the population including both OA and RA, the fact that  
5 two comparators were included, and the fact that there were  
6 minimal exclusions, and as has been pointed out, significant  
7 renal or hepatic dysfunction, baseline occult GI bleeding,  
8 and in the absence of an exclusion of aspirin as has been  
9 discussed.

10 [Slide.]

11 In terms of the study duration, a quote from the  
12 original protocol states that, "The trial will continue  
13 until the anticipated number of clinically significant upper  
14 GI events have been observed in both studies. Minimum  
15 participation for an individual is 26 weeks and maximum  
16 study participation is 52 weeks."

17 [Slide.]

18 So, in summary, the study was well designed and  
19 included several important components. It addressed the  
20 issue of chronic exposure to assess chronic safety. High  
21 dose to assess the robustness of any safety claim. Multiple  
22 comparators in an attempt to address generalizability.

23 Rigorous and well-defined endpoints, and the large  
24 trial size allowed for comparative data on overall safety  
25 including uncommon toxicities.

1 [Slide.]

2 I will briefly review the results.

3 [Slide.]

4 These are the results from the primary endpoint,  
5 that being complicated ulcer in the entire population, and  
6 as the cumulative rates indicate, there was no meaningful  
7 difference between the three groups.

8 [Slide.]

9 Next, there will be a graph of the time to  
10 complicated ulcer, a survival analysis, again using the  
11 traditional definition for the entire population.

12 [Slide.]

13 The only point to make here is that events  
14 continued to accrue throughout the study period in the  
15 Celebrex group, which is highlighted here, while the  
16 diclofenac group experienced only one event beyond the  
17 three-month period, and the ibuprofen group accrued no  
18 further events after approximately a half a year.

19 [Slide.]

20 In terms of the subanalyses for the complicated  
21 ulcer endpoint, non-aspirin and aspirin users.

22 [Slide.]

23 For the non-aspirin users, the results are shown  
24 here, and there was no statistically significant difference  
25 between diclofenac and Celebrex. There was a numeric

1 difference between ibuprofen and Celebrex. This is an  
2 uncorrected p-value, and it is put here to give a sense of  
3 magnitude of difference, however, it doesn't have the same  
4 statistical rigor as a prespecified endpoint since multiple  
5 comparisons were made before getting to this comparison.

6 [Slide.]

7 Again, the survival curve for the complicated  
8 ulcer in non-aspirin users.

9 [Slide.]

10 A similar pattern although obviously, fewer events  
11 through the study period, but again, events were early in  
12 the NSAID comparators, and the majority were early in the  
13 Celebrex group, as well, however, events did continue to  
14 accrue throughout the course of the study.

15 [Slide.]

16 For the aspirin users, the cumulative rates are  
17 displayed here. There is no statistical difference between  
18 the groups. There was a paradoxical finding in the  
19 ibuprofen group in that the rate was, in fact, lower than  
20 the other traditional NSAID comparator in Celebrex.

21 It is important to note that while a denominator  
22 of 412 is large for an efficacy study for an analgesic, for  
23 a large outcome study, this is not a large sample size and  
24 only one event in that sample size, so this may be  
25 hypothesis generating, but it should be looked at in the

1 context.

2 [Slide.]

3 Summarize the findings for complicated ulcers.

4 For the primary analysis, no differences between Celebrex  
5 and NSAIDs combined or individually was demonstrated.

6 For non-aspirin users, there was a strong trend  
7 favoring Celebrex compared to ibuprofen, however, no  
8 difference was shown between Celebrex and diclofenac.

9 Finally, in the analysis of aspirin users, no  
10 differences between Celebrex and diclofenac were shown.

11 There was a paradoxical trend favoring ibuprofen compared to  
12 both Celebrex and diclofenac, but once again, important  
13 caveats relate to the sample size, the fact that the study  
14 was not stratified for aspirin use, so there may be  
15 differences that we don't see in these results.

16 [Slide.]

17 Now, to discuss other relevant analyses  
18 specifically the composite endpoint of symptomatic  
19 complicated ulcers, just to point out in the original  
20 protocol, it states that, "Symptomatic upper GI ulcers,  
21 documented by endoscopy or upper GI barium x-ray with no  
22 evidence of perforation, bleeding or obstruction will be  
23 categorized and summarized separately."

24 So, the composite endpoint was not a prespecified  
25 endpoint.

1 [Slide.]

2 It is, as has been discussed, an important and  
3 certainly clinically relevant endpoint, and the  
4 ascertainment of these events was prespecified.

5 [Slide.]

6 For the entire population for this endpoint, the  
7 results are shown here. There was no meaningful difference  
8 between the diclofenac and Celebrex group with a very strong  
9 trend in favor of Celebrex compared to ibuprofen. Once  
10 again, this is a nominal p-value for an analysis that was  
11 not prespecified.

12 [Slide.]

13 Now, we will look at the survival curve, that  
14 endpoint, and this is somewhat different than the pattern  
15 that was seen for the primary analysis of complicated ulcers  
16 in that all three groups continued to accrue events going  
17 far out into the study.

18 [Slide.]

19 For the non-aspirin users, again, the cumulative  
20 rate. There was no meaningful difference between the  
21 Celebrex and the diclofenac group, where again there was a  
22 strong trend--this is the nominal p-value--for the ibuprofen  
23 group compared to the Celebrex group.

24 [Slide.]

25 The time to endpoint survival curve for the non-

1 aspirin users is displayed here, and the diclofenac and  
2 Celebrex groups virtually overlap, but they clearly separate  
3 out from the ibuprofen group shown here.

4 [Slide.]

5 Now, for the aspirin users, although the rates are  
6 higher in all groups compared to non-aspirin users or the  
7 entire cohort, the flip pattern between ibuprofen and the  
8 other comparators is seen similar to what was seen in the  
9 primary analysis of complicated ulcers. There is no  
10 statistically significant difference between the groups  
11 here, but nominally, the ibuprofen group, rather than being  
12 higher, is actually slightly lower here.

13 [Slide.]

14 Conclusions of this analysis of the composite  
15 endpoint. There was prespecified ascertainment of data, but  
16 the endpoint was not prespecified. As mentioned, it is  
17 clearly a clinically relevant endpoint.

18 There was a strong trend in favor of Celebrex  
19 compared to ibuprofen in the non-aspirin users with no  
20 difference demonstrated between Celebrex and diclofenac in  
21 the non-aspirin users.

22 [Slide.]

23 In aspirin users there was a paradoxical trend  
24 favoring ibuprofen compared to both Celebrex and diclofenac  
25 similar to the pattern that was seen at the primary endpoint

1 of complicated ulcers.

2 [Slide.]

3 Now, briefly, I will show one slide using this  
4 alternate definition, which was a prespecified definition,  
5 although not the primary analysis. Again, sign of GI  
6 bleeding be it hematemesis, melena or hemoccult-positive  
7 stool n the face of gastroduodenal ulcer erosion was  
8 required plus signs of a major bleed, which would include  
9 either a greater than 2 gram drop in hemoglobin once  
10 hydration after an acute event had taken place, or if  
11 transfusion was required acutely before equilibration of  
12 final hemoglobin less than or equal to the pre-bleed level,  
13 or orthostatic hypotension or a supine blood pressure of  
14 under 90/60.

15 [Slide.]

16 So, as you can see, this is a much smaller set  
17 that are likely to meet this definition, and there was no  
18 statistically significant difference seen between the groups  
19 at this endpoint.

20 [Slide.]

21 In terms of the high risk populations, as has been  
22 discussed earlier, age greater than 75, history of upper GI  
23 bleed, and aspirin use were all associated with a  
24 substantially higher relative risk compared to those that  
25 were not in each of these categories. This is univariate

1 here. The relative risk extends across both comparators.

2 [Slide.]

3 For the composite endpoint, symptomatic and  
4 complicated ulcers, the same general trend is seen with a  
5 substantially higher relative risk for those that meet each  
6 of these criteria compared to those that don't.

7 [Slide.]

8 Now, when considering high risk populations, you  
9 have to take into account an associated risk that is related  
10 to the underlying risk factor versus an attributable risk  
11 associated with the therapy.

12 If age and history of ulcer complications are  
13 independent risk factors separate from NSAID use for ulcer  
14 disease, then, the findings of high risk in association with  
15 the therapy may represent the intrinsic underlying risk  
16 rather than a drug effect or causality.

17 On the other hand, it is possible that there is an  
18 interaction between the underlying risk factor and the drug  
19 related risk, such that an exaggerated or a higher risk that  
20 is, in fact, attributable to therapy would need to be  
21 considered, in which case there would be causality.

22 [Slide.]

23 The overall conclusions. No statistically  
24 significant differences were shown for the entire population  
25 for the primary endpoint of complicated ulcer between

1 Celebrex and the NSAID comparators combined or individually.

2 An important relevant endpoint of the composite of  
3 symptomatic and complicated ulcers suggested a difference  
4 between Celebrex and ibuprofen in favor of Celebrex. No  
5 difference was seen between Celebrex and diclofenac.

6 [Slide.]

7 Hypothesis-generating findings include the fact  
8 that co-administration of aspirin was associated with an  
9 increased and similar risk of complicated ulcers in both  
10 Celebrex and diclofenac group in the range of 4-fold.

11 The same trend was seen at both the primary  
12 analysis and the composite endpoint analysis.

13 [Slide.]

14 The ibuprofen group that required low dose aspirin  
15 experienced a lower rate of complicated ulcers than either  
16 of the other two groups. Again, this trend was consistent  
17 between the two analyses.

18 [Slide.]

19 It is unclear whether these paradoxical findings  
20 associated with the concomitant use of aspirin and ibuprofen  
21 simply represent random findings or whether they represent a  
22 true differential interaction between aspirin and NSAIDs in  
23 terms of the upper GI toxicity.

24 [Slide.]

25 Further study is needed to clarify the safety of

1 co-administration of aspirin and NSAIDs COX-2 selective  
2 agents.

3 No conclusions regarding the safety of Celebrex  
4 compared to traditional less selective COX inhibitors as a  
5 group are possible.

6 Thank you.

7 DR. HARRIS: We will next hear from Dr. Witter.

8 **Medical**

9 **James P. Witter, MD., Ph.D.**

10 DR. WITTER: Let me first start by saying I am  
11 glad to know that others beside the agency utilize acronyms.

12 [Slide.]

13 As you know, CLASS stands for Celecoxib Long-term  
14 Arthritis Safety Study. By agreement, what I will be  
15 discussing is the entire database. Should you see any  
16 asterisks on any of the numbers, it indicates a level at a p  
17 .05, less than .05, and what I am going to try and do is  
18 summarize the data rather than try and regurgitate it, and  
19 get into a bit more discussion of the aspirin subgroups, so  
20 we will see if I am successful.

21 [Slide.]

22 Again, just to reiterate some of the basic of the  
23 CLASS protocol is that it was a combination of two  
24 protocols, Study 035, which has its NSAID comparator  
25 ibuprofen, and Study 102, which had diclofenac as its NSAID

1 comparator.

2 Celecoxib, as we now know, was used at the 2x  
3 dose, which as it turns out is the 1x dose for FAP.

4 It was a large study conducted in 386 sites  
5 throughout the U.S. and Canada involving, as we now know,  
6 almost 8,000 patients.

7 [Slide.]

8 The inclusion criteria--and I think we need to  
9 redefine when we say large and simple trials, we have to  
10 come up with something else because I think we appreciate  
11 that these are very complex results that we have gotten  
12 here, and the intent was, as you have heard several times,  
13 to make this as a real world as possible, and I am sure some  
14 of the discussion will center around whether that was  
15 successful or not--but really, the inclusion criteria  
16 included those who were old enough to give written informed  
17 consent.

18 You have to have OA or RA for about three months  
19 duration, and you then you needed to have an NSAID type  
20 compound, and that you were not pregnant.

21 The exclusion criteria were also similarly simple  
22 although they excluded folks with GI disease or ulceration  
23 actively or that had significant renal hepatic disease or  
24 coagulation defect and active malignancy, but again, how  
25 this represents the real world might be a point of

1 discussion later.

2 [Slide.]

3 The baseline demographics, whether you like to  
4 look at means or medians, was approximately 60 years in  
5 terms of age, there were about 11 percent of the patients  
6 that were 75 years or older.

7 This study was conducted primarily in white  
8 females. Approximately 27 percent of patients had RA, 10  
9 percent of patients had a history of either GI bleed or  
10 gastroduodenal ulcer, and about 21 percent were taking  
11 aspirin for cardiovascular prophylaxis.

12 [Slide.]

13 Again, just to reiterate, the use of concomitant  
14 medications, things like NSAIDs, either Rx or OTC were  
15 prohibited, but as we heard, there were a substantial number  
16 of patients who did use these things primarily for things  
17 like headaches and other reasons in the short term. If it  
18 was long term, they were excluded. Prohibited also were  
19 anti-ulcer drugs and antibiotics as they might be utilized  
20 to treat for H. pylori.

21 Allowed were, as we now know, aspirin, antacids  
22 for treatment for prophylaxis for osteoporosis, things like  
23 methotrexate and corticosteroids for the patients with RA,  
24 and then analgesics ranging from Tylenol to oxycodone on an  
25 as-needed basis, again with the idea to keep folks in the

1 trial.

2 [Slide.]

3 Just a bit about aspirin use in the CLASS trial.

4 It was, as we know, at 325 or less mg on a daily basis, and  
5 again it was for those who were at risk for certain events.  
6 However, as Dr. Goldkind indicated, it was not stratified in  
7 the CLASS study. Therefore, the dose and duration may have  
8 varied in the study with regard to this endpoint.

9 I think probably the safest thing to say is that  
10 no conclusions regarding aspirin co-use can be drawn from  
11 the CLASS study, but some interesting observations and  
12 potentially possible directions for future studies, which  
13 again may be part of our discussion this afternoon.

14 [Slide.]

15 Statistical issues, just to summarize, was the  
16 null hypothesis, that celecoxib was, in fact, equal to  
17 NSAIDs for the primary outcome of complicated ulcers.

18 It was estimated that there were going to be 40  
19 events, 8 in the roughly 4,000 celecoxib patients, 32 in the  
20 roughly 4,000 NSAID patients. It was assuming a withdrawal  
21 rate of 35 percent, power to 90 percent, and there was  
22 significance at 0.05 on two-sided testing.

23 [Slide.]

24 Now, again, what I am trying to do is simplify the  
25 data. I don't want to get into a line listing kind of

1 approach because we have seen lots of data, and I don't have  
2 any substantial differences from the sponsor on their  
3 numbers.

4 So, of the folks that are in the ITT population,  
5 we can see here that more people tended to complete the  
6 study in the diclofenac group, whereas, more tended to be  
7 withdrawn in the ibuprofen group.

8 What is not up here are the reasons, and I think  
9 we discussed that a bit earlier. For ibuprofen, there was  
10 more that left the trial for treatment failure of  
11 noncompliance, whereas, in the diclofenac group there were  
12 more that left because of adverse events. Interestingly and  
13 refreshingly, there were no patients lost to follow up,  
14 which is something we seem to be discussing a lot at these  
15 venues.

16 [Slide.]

17 Now, admittedly, efficacy in the CLASS trial was  
18 not an endpoint, but I think it is worthwhile just spending  
19 a little time to review this. If one looks at patient  
20 globals, patient assessment of pain on the VAS scale, the  
21 disability indices of health assessment questionnaire or the  
22 generic SF-36 or patient withdrawal rates, if those are  
23 measures of efficacy, then, what we can say is that  
24 celecoxib as utilized in the CLASS trial was not shown to be  
25 more effective than NSAIDs.

1           However, there was an interesting trend if you  
2 compared against the original database of less patients  
3 being withdrawn in the CLASS trial than the NDA, suggesting  
4 that there may, in fact, be some utility to a higher dose  
5 for a time period.

6           [Slide.]

7           Now, I am not going to go through all the GI  
8 summary, all the data, I am just going to try and summarize  
9 it, and again to reiterate that the primary endpoint was  
10 that of complicated ulcers in contrast to symptomatic  
11 ulcers, and there were 38 of these events which are  
12 uncensored. This was looking at all the three groups.

13           Celecoxib was not statistically significantly  
14 different than either of the individual NSAIDs or pooled  
15 NSAIDs, so therefore, celecoxib did not meet the primary  
16 endpoint of this trial, and there is no disagreement on  
17 that.

18           [Slide.]

19           However, when you look at the primary endpoint in  
20 a more restrictive fashion, and in particular what I am  
21 referring to here is those folks who were not taking  
22 aspirin, there were a total of 22 uncensored events in all  
23 the groups, and in this case, celecoxib was different with a  
24 nominal p-value of 0.03, and as Dr. Goldkind had indicated,  
25 this was not corrected for multiplicity, nor was this a

1 prespecified endpoint, but it was different than ibuprofen,  
2 but not diclofenac.

3 [Slide.]

4 When the endpoints were expanded to include, as we  
5 now know, complicated and symptomatic ulcers, there were 105  
6 events in all groups, and here again celecoxib was able to  
7 show that it was better than ibuprofen, but not diclofenac.

8 When we take that expanded population of  
9 complicated and symptomatic ulcers, and then look at only  
10 the aspirin non-users, there were 59 events, uncensored  
11 events in all the group, and once more, celecoxib did show  
12 that it was better than ibuprofen, but not diclofenac.

13 So, a consistent finding here is that under no  
14 circumstances of patient group, length of trial, was there  
15 any difference between celecoxib and diclofenac.

16 [Slide.]

17 Again, I am trying to get a little different spin  
18 to the data here rather than just repeat what we have seen.

19 So, looking at GI adverse events and looking at  
20 all patients, those that did take aspirin, those that didn't  
21 take aspirin, it can be seen here that whether we look at  
22 the data in terms of any adverse events, or any of those  
23 adverse events leading to withdrawals, and it doesn't matter  
24 what patient population we look in, whether it is all  
25 patients in the aspirin users or in the non-aspirin users,

1 there were more of these events in the diclofenac group.

2 Also, it certainly seems to point out the effects  
3 of aspirin as you look across and compare aspirin to non-  
4 aspirin, the event rate is higher in the aspirin users  
5 across the board.

6 [Slide.]

7 Now, looking at all adverse events and going back  
8 to what we just saw with the GI slide, we can see here that  
9 looking at any adverse event or severe adverse events, or  
10 adverse events that led to withdrawal, once again, the  
11 highest incident rates were in the diclofenac group.

12 However, when you look at the serious adverse  
13 events, there was a higher rate in the celecoxib group, and  
14 if you are wondering about the differences in numbers, these  
15 are as percentage, the sponsor presented it as patient year  
16 data before.

17 [Slide.]

18 Deaths, it certainly could be argued one of the  
19 most serious adverse events there is in a trial, there were  
20 36 all-cause deaths in this trial. There were 19 in the  
21 celecoxib group, which comes out to be 0.5 percent, 9 in the  
22 diclofenac group, which is 0.5 percent, and 8 in the  
23 ibuprofen group, which comes out to be 0.4 percent.

24 Most of these deaths were in patients age 65 years  
25 or older, and most of these were cardiovascular in nature.

1 That came out to be 58 percent in the celecoxib group, 56  
2 percent in the diclofenac group, and 63 percent in the  
3 ibuprofen group.

4 [Slide.]

5 Looking at this data in a slightly different way,  
6 on patient years and breaking it up into aspirin users and  
7 non-users once more, whether we look at all-cause mortality,  
8 whether we look at cardiovascular mortality, whether we look  
9 at it in aspirin users or non-aspirin users, celecoxib is no  
10 worse than any of the other comparators.

11 [Slide.]

12 Turning to renal adverse events--and again my  
13 attempt here is to simplify the data--whether you look at  
14 any event or any of those events that led to withdrawal,  
15 there was a higher incidence of these events in the  
16 ibuprofen subgroup.

17 If you look at the data, which we have asked the  
18 sponsors to do, in a contingency type approach, for example,  
19 where you have increases of BUN and/or creatinine above the  
20 level specified here, we see that there are more of these  
21 types of events in the diclofenac group.

22 [Slide.]

23 Looking at cardiovascular events, and in this  
24 particular slide, again for simplicity, I have combined the  
25 categories into edema, which, for example, represent the

1 line listings of edema, peripheral edema or generalized  
2 edema, anginal disorders, and thrombophlebitis, again, these  
3 are combination, it is more of a mixed picture.

4           You can see, for example, that in terms of edema,  
5 there tends to be more events in the ibuprofen group,  
6 whereas, with anginal disorders, there tends to be more in  
7 the ibuprofen group, it doesn't whether aspirin or not, and  
8 in looking at thrombophlebitis and the events in that  
9 category, again, it is a mixed picture, in aspirin users  
10 more in diclofenac, non-aspirin users, more so in the non-  
11 aspirin users.

12           [Slide.]

13           Looking at serious cardiovascular events--and  
14 again I have combined categories here, somewhat similar to  
15 the last one although there is atrial added in here--and  
16 this time just focusing in on the non-aspirin population,  
17 there appear to be slightly more events in the atrial,  
18 anginal, and MI categories for celecoxib as compared to the  
19 other groups. However, this is not the case for the  
20 combined thrombophlebitis type events.

21           The aspirin data, I don't have it here, but it is  
22 a mixed picture, and in none of the categories is celecoxib  
23 leading or have the highest incident rates compared to the  
24 others.

25           [Slide.]

1           Turning to hepatic adverse events, if you look  
2 again at any adverse event or any adverse event leading to  
3 withdrawal, we once again see that diclofenac has the  
4 highest rate, and what I have done here is again looking at  
5 a contingency type of approach, and looking at multiples  
6 above the upper limit of normal, so, for example, the liver  
7 enzymes AST or ALT combined or combining one of those  
8 enzymes with alkaline phosphatase or total bilirubin or  
9 doing those alkaline phosphatase and bilirubin together,  
10 once again we see that there are more events in the  
11 diclofenac group, and I think this data nicely suggests that  
12 whatever the problem is, it is in the liver.

13           [Slide.]

14           Looking at adverse events that impact the skin,  
15 whether you are discussing it in terms of rash or pruritus,  
16 looking at the overall events or those events that led to  
17 withdrawal, there were more of these events in the celecoxib  
18 group. However, for the most part, these were not severe  
19 reactions.

20           [Slide.]

21           Now, just trying to summarize a little bit of the  
22 aspirin data--and again I think we are only looking at these  
23 just as some observations, but interesting nonetheless--as  
24 Dr. Goldkind had indicated, whether you look at the  
25 complicated ulcers, and actually I should have had up here

1 symptomatic ulcers, as well, we saw that aspirin co-use with  
2 celecoxib and diclofenac led to an increase in these events,  
3 but there seemed to be a paradoxical, which is the term that  
4 we are using, decrease or lessening of events with  
5 ibuprofen.

6           However, when you look at GI adverse events or  
7 withdrawals because of an adverse event, consistently across  
8 the board you see that co-use of aspirin increased the  
9 events in all three groups.

10           [Slide.]

11           When you look at cardiovascular events, we have  
12 what I will call here a mixed picture. In terms of overall  
13 mortality, we see that it increases with celecoxib and  
14 diclofenac, but it appears to go down with diclofenac.

15           In terms of MI, it goes up in all three groups,  
16 but if you look at thrombophlebitis, it goes up in  
17 diclofenac and ibuprofen, but it appears to go down in the  
18 celecoxib groups. So, aspirin, as I say, has some  
19 interesting, but not necessarily consistent results.

20           [Slide.]

21           So, overall safety in terms of the GI tract, once  
22 more, celecoxib was unable to demonstrate a statistical  
23 superiority to either ibuprofen or diclofenac when  
24 considering the primary endpoint of the CLASS trial.

25           However, celecoxib was able to demonstrate a trend

1 in superiority to ibuprofen (only) in patients not taking  
2 aspirin and with broader endpoints meaning particularly  
3 complicated and symptomatic ulcers.

4 [Slide.]

5 In terms of renal safety, celecoxib does not  
6 effect acid-base balance more than diclofenac or ibuprofen.  
7 I should note that this is a fulfillment of a Phase IV  
8 commitment by the sponsor.

9 There does not appear to be any large effect on  
10 renal adverse events relative to ibuprofen or diclofenac.

11 Although it is not seen in the CLASS trial,  
12 serious renal disease, such as acute renal failure or  
13 interstitial nephritis, are in the current labeling for  
14 Celebrex.

15 [Slide.]

16 In terms of cardiovascular in the CLASS trial,  
17 there was no apparent adverse effect on cardiovascular  
18 mortality or serious adverse events related to thrombosis  
19 relative to ibuprofen or diclofenac, although this does not  
20 exclude that there is some kind of a lesser cardiovascular  
21 effect as I think we have heard this morning.

22 However, events such as myocardial infarction,  
23 congestive heart failure, ventricular fibrillation,  
24 pulmonary embolism, cerebral vascular accident, vasculitis  
25 and other events are in the current label for Celebrex.

1 [Slide.]

2 Hepatobiliary safety. Adverse events are not more  
3 frequent than seen with ibuprofen or diclofenac, and  
4 although not seen in the CLASS trial, such events as  
5 hepatitis, jaundice, and liver failure are in the label.

6 [Slide.]

7 In terms of skin, rash and pruritus, as I pointed  
8 out earlier, are generally mild to moderate, are important  
9 adverse events that frequently lead to withdrawal with this  
10 compound. Once again, serious adverse events, such as  
11 Stevens-Johnson syndrome, toxic epidermal necrolysis or  
12 erythema multiforme, again, they are in the label.

13 [Slide.]

14 Overall safety in terms of deaths, there were no  
15 deaths from hepatobiliary, renal, dermatologic, or GI  
16 causes. The latter, I find particularly interesting.

17 Deaths from the cardiovascular causes appear to  
18 reflect more the population studied rather than any new  
19 adverse effect of celecoxib, and the deaths from  
20 cardiovascular causes are not more common in the celecoxib  
21 group as compared to the controls.

22 [Slide.]

23 Trying to make a grand summary, then, of the  
24 overall safety of celecoxib, in this case what I am going to  
25 do is look all the way from the NDA and through to the

1 current data, it appears that celecoxib looks more like an  
2 NSAID than placebo.

3 [Slide.]

4 Finally, as I had discussed earlier, and we still  
5 I think tend to want to do this, make comparisons against  
6 NSAIDs and COX-2's, particularly in regards to safety, so I  
7 am wondering here what is the best way to look at the data.  
8 For example, is beating one NSAID the same as beating them  
9 all? On the other hand, is losing to one NSAID the same as  
10 losing to them all?

11 Thank you very much.

12 DR. HARRIS: Thank you, Dr. Witter.

13 Are there any comments, questions related to  
14 clarification from the committee? Yes, Dr. Sampson.

15 DR. SAMPSON: Dr. Witter, I was wondering if you  
16 could just say a few more words about what you call the null  
17 hypothesis of Celebrex being equal to "NSAIDs"? At least  
18 when I read the material, it looks to me like there is two  
19 null hypotheses as opposed to some sort of a composite, and  
20 the two null hypotheses are Celebrex versus ibuprofen, and  
21 Celebrex versus diclofenac.

22 Are I misunderstanding that is some sense?

23 DR. WITTER: I think the first go-around was to  
24 look at the combined NSAID groups and then to look at the  
25 individual compounds to preserve the type 1 error.

1 DR. SAMPSON: At least my reading of the  
2 statistical issues, the overall test was just an artifice to  
3 protect the other conclusions, it was never really intended  
4 as a scientific null hypothesis at least from my  
5 understanding of it. Maybe I need to be corrected on that.

6 DR. GOLDKIND: I think that that is true. It was  
7 a stepwise approach, but the primary hypothesis was related  
8 to step 2 rather than step 1, and statistically, if the  
9 first step failed, one would not go beyond that, and so in a  
10 simple sense, one would not have gone beyond that first null  
11 hypothesis of the group comparisons for that endpoint.

12 DR. SAMPSON: And if the first step were a  
13 success, one wouldn't then conclude that you were superior,  
14 quote, "to NSAIDs."

15 DR. GOLDKIND: The spirit of the study was to look  
16 to see how generalizable it is, so looking at the individual  
17 NSAIDs was the intent.

18 DR. HARRIS: Yes, Dr. Wofsy.

19 DR. WOFSY: I think I have a similar question in  
20 regard to your last comment. I wonder if you could amplify  
21 on, you said celecoxib looks more like an NSAID than like  
22 placebo, but there is no placebo in these data.

23 How do you come to that conclusion? Maybe to  
24 broaden the question, if the issue in this study was to look  
25 at whether or not the GI labeling was necessary, that is, is

1 there a GI risk compared to placebo, how do we address this  
2 question in a study that has no placebo?

3 DR. WITTER: The slide had in there that was  
4 including the discussion of the NDA material, in which case  
5 there were a lot of placebo controls, and I was trying to go  
6 back to the original presentation where were always looking  
7 at how these compounds compared, not only against NSAIDs,  
8 but also against placebo.

9 We had a substantial discussion, for example, in  
10 terms of GI events, whether these rates would look like  
11 placebo, so that comment was meant to kind of be a broad  
12 sweeping compilation of all the data from the NDA up and  
13 including the CLASS trial and looking at all the safety  
14 parameters, be they GI events, renal events, as I discussed,  
15 because that has always been kind of an issue is the overall  
16 safety profile of these compounds, what is the best way to  
17 view them.

18 DR. HARRIS: Any other comments? Yes.

19 DR. SAMPSON: One further clarification. In  
20 patients not taking aspirin, it was indicated that there was  
21 a trend, and the p-value is 0.03 of Celebrex versus  
22 ibuprofen, and just for my own clarification, I understand  
23 this wasn't a preplanned analysis and thus would not  
24 necessarily be subject to the multiple comparison  
25 procedures, however, if one were to use the multiple

1 comparison procedure and do the simultaneous test against  
2 the NSAIDs, I think you wouldn't come down to this level to  
3 do this test, is that correct? That is, in aspirin users  
4 using the primary endpoint, you don't show a difference  
5 between Celebrex and "NSAIDs," or am I not remembering the  
6 data?

7 DR. GOLDKIND: Are you referring to the non-  
8 aspirin users or aspirin users?

9 DR. SAMPSON: Non-aspirin users.

10 DR. GOLDKIND: We will let our statistic team  
11 leader address that.

12 DR. LIN: I think the issue here is that the  
13 primary endpoint did not come out, so, you know, there is a  
14 question what procedure that you would use to look at these  
15 other endpoints, so the p-value of 0.0037, if you really  
16 follow the stepwise procedure or not, I mean that is not  
17 totally clear.

18 I think Jim's point was simply that that was a  
19 nominal p-value without concerning the overall difference  
20 between celecoxib and the overall NSAID groups.

21 By the way, when Jim put up the slides about the  
22 null hypothesis that celecoxib was the same as NSAIDs, I  
23 think the hypothesis really meant to say that the null  
24 hypothesis is that celecoxib is the same as ibuprofen, and  
25 is the same as diclofenac in terms of GI outcomes, so that

1 if you reject the null hypothesis, you would have the  
2 possibility that celecoxib is better than ibuprofen or  
3 celecoxib is only better than diclofenac, or both.

4 DR. HARRIS: Dr. Nissen.

5 DR. NISSEN: In terms of the breakdown of the  
6 cardiovascular events, you know, we tend to think of them in  
7 several groups. One is the incidence of stable angina, and  
8 so on, and the other is the incidence of events that we  
9 suspect are related to plaque rupture with a thrombus.

10 So, when I looked at the data, I was adding  
11 together in my mind the unstable angina and acute MI groups,  
12 because both disorders we suspect are in most cases due to  
13 plaque rupture with a thrombus.

14 I don't think these reached statistical  
15 significance when you pool them, but there certainly are  
16 some trends here where if you add the unstable angina and  
17 the MI in the celecoxib group there were 27 events, in the  
18 diclofenac group there were 8, in the ibuprofen there were  
19 9. So, there is this issue obviously we have to deal with  
20 today and tomorrow about whether there is either an absence  
21 of an antiplatelet effect or even a pro-thrombotic effect.

22 I wonder if you have any thoughts about that based  
23 upon your looking at the data.

24 DR. WITTER: Whether there is a difference or  
25 whether there is--

1 DR. NISSEN: Well, there is a trend obviously, I  
2 think there is some trending here.

3 DR. WITTER: Right. There are certain trends, and  
4 I tried to point out some of the trends in my presentation,  
5 as well, that are suggestive that there is an effect on  
6 endpoints as you have just alluded to, but when you look at  
7 the data in aggregate, it doesn't seem like there is any  
8 apparent effect. Whether that is related to the powering of  
9 the study, which is probably the main issue, or something  
10 else, I think it is hard to tease out of this.

11 DR. PINA: Something that is probably hard to  
12 tease out, too, is going back now to the cardiovascular  
13 events and edema, rise in BUN and creatinine and potassium,  
14 which is a big concern, there seems to be a trend--this is  
15 from Dr. Throckmorton's analysis from Cardioresenal-- between  
16 the patients who are on aspirin regardless of which NSAID  
17 they are on, and a high potassium over 5.

18 Do you have any comments on that, because that is  
19 obviously of great significance to us with the concomitant  
20 drugs that we are using, which also now elevate potassium?

21 DR. WITTER: I am obviously aware of Dr.  
22 Throckmorton's review, and unfortunately, he couldn't be  
23 here today, although we had requested that. We discussed  
24 that data in particular, as well as all the other data at  
25 great length, and I think what we came down to is that

1 although it appears to be an observation, as you have just  
2 pointed out, its clinical significance is difficult to put  
3 into place. We weren't sure how to actually look at this  
4 from a clinical perspective. Although there was a trend for  
5 higher potassium levels in the celecoxib groups, its  
6 clinical significance to us is unknown at this point in  
7 time.

8 DR. PINA: I think that goes back to my original  
9 question about the concomitant use of other drugs, such as  
10 ACE inhibitors in this group, which we are going to see  
11 going up after the results of the HOPE trial. It is exactly  
12 the same population, and now with the greater use of  
13 aldactone in this population, sometimes appropriately,  
14 sometimes not, but hyperkalemia is becoming a real problem,  
15 and this is the very population that has osteoarthritis, so  
16 that is clinically of great concern to me.

17 DR. WITTER: Right. I mean one of the things that  
18 we are looking for in the discussion today and tomorrow are  
19 these kind of comments in terms of how to look at the data,  
20 and particularly also how might it help us then design  
21 future trials, but your point is well taken.

22 DR. HARRIS: Dr. Witter, if I may ask again about  
23 the rise in potassium, my understanding, I saw a comment  
24 that, in fact, because I am trying to determine how real  
25 this was, that in several instances they were bracketed by

1 normal potassium values. Was that frequent enough?

2 DR. WITTER: That was one of the reasons that we  
3 couldn't, Dr. Throckmorton and myself, couldn't come to a  
4 full clinical understanding of those values, if they were,  
5 as you say, bracketed by normal values.

6 I think we all know that to get an abnormal  
7 potassium value on occasion is not that uncommon. So, that  
8 kind of endpoint, we didn't know again what to do with this  
9 particular data.

10 DR. HARRIS: Thank you.

11 Now we come to the open public hearing. There is  
12 only one presenter who registered, and that is Dr. Sidney  
13 Wolfe.

#### 14 Open Public Hearing

15 DR. S. WOLFE: Thank you.

16 The two things I wanted to discuss are the GI  
17 toxicity and at somewhat more length and with one minor  
18 exception just on celecoxib and general principles. One  
19 exception is just an allusion to Vioxx, more of that  
20 tomorrow since we are just now obtaining some of the data.

21 As this committee knows well, despite apparently  
22 large differences between the more traditional COX-1  
23 inhibiting NSAIDs as far as the occurrence of perforations,  
24 ulcers, and GI bleeding, the committee and the FDA decided  
25 on identical class labeling for all of these older NSAIDs

1 which warns about these serious and not infrequent adverse  
2 effects.

3           When the approval of celecoxib and rofecoxib were  
4 being considered, we stated that there needed to be clear  
5 evidence from comparative long-term, higher dose randomized  
6 trials in which celecoxib, rofecoxib or any other COX-2 type  
7 of anti-inflammatory drug is compared to the least dangerous  
8 of these older drugs, to find out if there is a  
9 statistically significantly lower amount of serious GI  
10 complication, such as perforations, ulcers or bleeding with  
11 the COX-2 inhibitor drug.

12           Unless this evidence is produced, we said that  
13 there is no more reason, according to the long-standing  
14 logic of this committee, to spare any COX-2 inhibitor from  
15 the class label now applied to all of the other NSAIDs than  
16 there is to distinguish between the members of this older,  
17 COX-1 predominant class.

18           Now that somewhat more definitive studies  
19 comparing the risks of serious GI complications of celecoxib  
20 and rofecoxib with other NSAIDs have been done, the evidence  
21 of statistically significant reduction in this serious  
22 complications in people using the two COX-2 inhibitors is  
23 still lacking.

24           We agree with the conclusions of FDA Medical  
25 Officer Dr. James Witter's review which found that,

1 "Celecoxib did not demonstrate statistical superiority to  
2 NSAIDs pooled or with the comparator diclofenac and  
3 ibuprofen with regard to the primary safety endpoints of  
4 CSUGIEs at any point in the trial although there were trends  
5 favoring celecoxib.

6 We also agree with the conclusions of FDA's Office  
7 of Postmarketing Drug Risk Assessment that the 73 deaths  
8 seen with celecoxib--36 of those were celecoxib, 37 with  
9 rofecoxib--from GI bleeding, obstruction, perforation or  
10 stenosis show that the current labeling for the two drugs  
11 "reflect the risk of fetal gastrointestinal bleeding,  
12 obstruction, perforation or stenosis."

13 Not frequently discussed is the fact that the COX-  
14 2 enzyme has other important physiological functions in  
15 addition to its role in inflammation. These include GI  
16 tract tissue repair, the inhibition of which may explain the  
17 serious GI toxicity seen with the drugs, epithelial  
18 integrity, cardiac repair after injury, renal vascular  
19 homeostasis, fetal renal development during pregnancy,  
20 ovarian function and fertility, and cartilage repair.

21 New classes of drugs such as celecoxib and  
22 rofecoxib offer not only new mechanisms of action, but also,  
23 by virtue of their inhibition of the important COX-2 enzyme,  
24 new mechanisms of potential toxicity and the possibility of  
25 a new spectrum of adverse effects.

1           Now, I will discuss for several minutes the  
2 failure of protection from heart attacks, the just recently  
3 referred to absence of an anti-platelet effect, and probable  
4 cardiac toxicity, a pro-thrombotic effect.

5           In an editorial accompanying the publication of  
6 the CLASS celecoxib enzyme study last fall, the authors, one  
7 of whom, Dr. Wolfe, is sitting at the table, the authors  
8 expressed concern about the theoretical possibility of  
9 damage by COX-2 inhibitors such as celecoxib and rofecoxib.  
10 They stated that "they might increase the risk for  
11 thromboembolic cardiovascular events because of the  
12 preferential inhibition of endothelial prostacyclin  
13 synthesis without corresponding inhibition of platelet  
14 thromboxane synthesis."

15           The editorialists stated, however, that they "did  
16 not believe that the trial, as published"--and I will go  
17 back to that in a minute--"showed evidence of this actually  
18 occurring."

19           I will now just spend a minute referring to a  
20 study which, in my view, is one of the most important  
21 studies published in the last 10 years on anything having to  
22 do with this topic.

23           It was published in the August 29th issue last  
24 year of the Proceedings of the National Academy of Sciences.  
25 As many of you know, the referees for this journal are the

1 members of the National Academy of Sciences. This paper was  
2 sent in by Gene Brownwall, formerly head of the National  
3 Heart Institute. When I was at NIH it was called that.

4           In this study, they looked at the ability of  
5 rabbits, conscious rabbits, to withstand temporary  
6 experimental coronary artery occlusion and found that it was  
7 significantly impaired by treatment with either celecoxib or  
8 NS-398, both of which COX-2 inhibitors completely blocked the  
9 cardioprotective effects of the COX-2 enzyme, so we are  
10 really talking about the importance of the COX-2 enzyme in  
11 the heart and why its inhibition by drugs like this may be  
12 dangerous.

13           The authors of that study concluded that the COX-2  
14 enzyme is a "cardioprotective protein", "plays an essential  
15 role in cardioprotection afforded by late phase  
16 preconditioning" and found that its inhibition in these  
17 circumstances was harmful, resulting in larger myocardial  
18 infarctions in the experimental setting.

19           The authors described late phase preconditioning  
20 as "an adaptive response of the heart to a mild ischemic  
21 stress (decreased blood flow) that confers relative  
22 resistance to a subsequent ischemic insult occurring 12 to  
23 72 hours later."

24           In the careful review of the data from the CLASS  
25 study, some, but not much of which was published in the JAMA

1 article, FDA Cardio-Renal Division reviewer Dr. Throckmorton  
2 found that "the incidence of adverse events related to  
3 cardiac ischemia (decreased blood flow to the heart) was  
4 higher in the celecoxib group...and was most pronounced in  
5 the group of patients not taking aspirin" as a  
6 cardiovascular protective drug.

7 In these patients, the rate of myocardial  
8 infarction was also highest in the celecoxib group (0.2  
9 percent) compared with users of the other two drugs (0.1  
10 percent). For all patients, on and off aspirin, there was a  
11 higher incidence of atrial fibrillation, a cardiac  
12 arrhythmia, in the celecoxib group than in either of the  
13 other two groups, again more pronounced in the group not  
14 taking aspirin.

15 The author concluded by stating that "the data do  
16 not exclude"--this is Dr. Throckmorton--"a less apparent  
17 pro-thrombotic (blood clot forming) effect of celecoxib,  
18 reflected in the relative rates of cardiac adverse events  
19 related to ischemia."

20 These apparent differences in cardiac toxicity  
21 seen in CLASS in which neither of the two comparator drugs  
22 is particularly effective, compared to aspirin, in  
23 decreasing the occurrence of heart attacks, were magnified  
24 in the VIGOR or rofecoxib/naproxen study by the fact that  
25 naproxen, compared with either ibuprofen or diclofenac, does

1 have a coronary protective effect similar to that of  
2 aspirin.

3 In the discussion of the rofecoxib study,  
4 explaining the difference between naproxen and drugs such as  
5 ibuprofen and diclofenac, the authors pointed out that these  
6 latter drugs, unlike naproxen, "do not produce sustained  
7 maximal inhibition of platelet aggregation."

8 In that study--and I said I will just refer  
9 briefly because of tomorrow's discussion, I think it is  
10 relative to just looking at all of the I believe  
11 accumulating evidence on the cardiac toxicity--in that  
12 study, there was a highly statistically significant increase  
13 in heart attacks in the overall rofecoxib group (0.4  
14 percent) compared to the naproxen group (0.1 percent).

15 This amounted to approximately 160 heart attacks  
16 with rofecoxib (out of 4,047 patients) compared with 40  
17 heart attacks with naproxen (out of 4,029 patients). This  
18 difference was most pronounced, as seen in the celecoxib  
19 study, in those not taking aspirin, but even in others,  
20 there was a 2-fold difference, which the paper said not  
21 statistically significant, which I believe needs to be  
22 disputed. Since the FDA has more access to data, it will be  
23 interesting to hear what happens tomorrow.

24 Although the authors stated this latter difference  
25 was not statistically significant, it may be incorrect. It

1 must be pointed out that this excess of 120 heart attacks in  
2 the celecoxib group dwarfed the advantage seen in the same  
3 study for complicated confirmed upper GI events for which  
4 there were 16 in the celecoxib group and 37, an excess of 21  
5 such events in the naproxen group.

6           There is little question that 120 more heart  
7 attacks in approximately 4,000 patients is a much more  
8 serious danger than 21 fewer complicated confirmed upper GI  
9 events.

10           Recommendations. Once again, a seemingly magical  
11 bullet seems to have self-destructed as research reveals the  
12 larger context in which it operates, the risks as well as  
13 the benefits. The benefits of COX-2 inhibitors as far as  
14 reducing GI toxicity appear to have been grossly exaggerated  
15 and oversold.

16           Years after the research on these benefits was  
17 done, a rapid accumulation of evidence on risks is  
18 occurring. For an important enzyme which is close to  
19 ubiquitous in the body, it is less than surprising that  
20 blocking its activity in one part, the GI tract, must be  
21 balanced against the apparently harmful effects of blocking  
22 its critical functions in other parts of the body, such as  
23 the heart.

24           Recommendations: 1. We strongly urge the  
25 retention of the NSAID class-warning label for these drugs,

1 possibly adding that there is no evidence of statistically  
2 significant reduction in serious GI toxicity, at least for  
3 celecoxib. This should take the form of a box warning (for  
4 all the drugs) which should be placed at the beginning of  
5 the label. Right now it's bold, no box warning, not at the  
6 beginning.

7           2. A second box warning about cardiovascular  
8 toxicity needs to be added. It should warn of the lack of  
9 platelet aggregation inhibition of the drugs which protects  
10 those at risk from an increased occurrence of heart attacks.

11           In addition, the evidence which is rapidly  
12 accumulating about the heart damage, the pro-thrombotic or  
13 what looks like effect, causes by these drugs must be  
14 mentioned in this cardiovascular box warning. We urge  
15 consultation with the Cardio-Renal Division of FDA--already  
16 have had some, but the whole division--and possibly with  
17 FDA's advisory committee to accomplish this task.

18           3. Finally, an FDA-approved Med Guide for all  
19 NSAIDs should be required.

20           I would be glad to try to answer any of your  
21 questions. I would strongly recommend looking at this paper  
22 on the Proceedings of the National Academy of Sciences. I  
23 have read it about 10 times, and it really has got lots of  
24 information very relevant to what seems to be unfolding  
25 here.

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.]

## AFTERNOON SESSION

[1:00 p.m.]

1  
2  
3 DR. HARRIS: In starting this afternoon's session,  
4 I want to remind members of the committee and advisors that  
5 when you speak, if you can give your name before you speak,  
6 since this is being transcribed, and once you have made your  
7 comment, to turn off your microphone.

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

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

15 Thank you.

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

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

23 So, I would like to ask Dr. Jerry Faich, who is  
24 the chairperson of our Data Safety Monitoring Board, to  
25 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. WOFSY: 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 hemocult-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 from 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. WOFSEY: 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. WOFSY: 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. WOFSY: 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

1 restated it now, but the very first time that we have not  
2 established it, but there is still room for doubt.

3 DR. HARRIS: Well, I don't want to prolong this  
4 discussion. I did want to ask one question, and that is, of  
5 course, if you are designing the warnings with respect to GI  
6 safety and significant sort of side effects with Celebrex,  
7 you know what the labels are now, and the question is has  
8 anything been presented to you today that would make us want  
9 to change that label, and we are acting entirely in an  
10 advisory capacity, of course.

11 DR. GEIS: Could I just beg your indulgence just  
12 for one moment just for one comment and just the ability to  
13 show one slide, if I could? I think the comments about  
14 retrospective changing definitions, I would just like to  
15 clarify that those endpoints were prospectively defined,  
16 just to clarify that.

17 And then just one slide on data that I think is  
18 meaningful from a GI point of view, that I would like to  
19 call the people's attention. If I could have Slide 933.

20 [Slide.]

21 This is the hemoglobin and hematocrit data that  
22 Dr. Lefkowitz showed in the earlier presentation, and what  
23 it is, is the percent of patients who had clinically  
24 significant reductions in hemoglobin and hematocrit during  
25 the study. So, these are all the patients, and we show it

1 in the non-aspirin users and the aspirin users in all three  
2 treatment groups.

3 You can see that there is a statistically  
4 significant reduction in the percent of people who had these  
5 GI blood losses in Celebrex versus diclofenac versus  
6 ibuprofen in non-aspirin users, and we also see it in the  
7 aspirin users.

8 You can also see that in each of the treatment  
9 groups, in celecoxib and in diclofenac. In the aspirin  
10 users, the reductions or the blood loss was greater due to  
11 the aspirin use than in the non-aspirin users.

12 So, we think that is really an important point  
13 that people should consider when considering clinical  
14 meaningfulness of GI safety.

15 Thank you.

16 DR. HARRIS: Thank you very much for that comment.

17 Perhaps I will allow just one other comment with  
18 respect to what was said. I mean the issue is does the  
19 demonstration of less blood loss, how does that translate  
20 into clinically meaningful GI events.

21 DR. M. WOLFE: The question that is raised is  
22 upper GI safety, and a study in the early nineties from  
23 Basil Hershwitz's group showed that 35 percent of blood loss  
24 is from the low ligament of Treitz. I am not saying this  
25 not true data, but we can't extrapolate to say that that

1 adds credence to the possibility of more upper GI safety  
2 based on that alone.

3 DR. CRYOR: Dr. Geis, in fact, I agree with you,  
4 and the slide that you just showed was a point that I raised  
5 earlier. Having said that, however, we have to prioritize  
6 these various endpoints, and your primary endpoint,  
7 prespecified endpoint, in my opinion, is a more clinically  
8 important endpoint than the one just demonstrated.

9 DR. HARRIS: Thank you very much, Dr. Cryor.

10 I want to push on. I think we have a sense with  
11 respect to the upper GI events. I will just touch on the  
12 question of global safety because we would look at each  
13 separately, and I am wondering if, in fact, I might start  
14 with one of our cardiologists, our experts here, to start  
15 the ball rolling.

16 Of course, global safety is much larger than that,  
17 but certainly the issue of cardiac safety is important.

18 DR. PINA: Attesting to global safety, I cannot  
19 say with any assurance that this drug has any benefit over  
20 the other nonsteroidals, and, in fact, there are some trends  
21 in the wrong direction for cardiovascular side effects.

22 I continue to be concerned with the hyperkalemia  
23 that tends to be demonstrated with potassiums less than 5,  
24 the edema, and the rise in BUN and creatinine, which I think  
25 are very meaningful to this group of patients who do not

1 have normal renal function to start with even though it may  
2 not be clinically apparent.

3 DR. HARRIS: Dr. Nissen.

4 DR. NISSEN: Looking at the data critically, it  
5 seems to me that we really have a tradeoff here, and it's  
6 the classical tradeoff. You know, there are trends toward  
7 fewer upper GI complications albeit not statistically  
8 significant, but there are trends.

9 There are somewhat fewer events in the upper GI  
10 tract with celecoxib compared to the older comparators, but  
11 there are also very similar sized trends toward more  
12 cardiovascular events. So, I think you just can't divorce  
13 the two from each other because to a patient it really  
14 doesn't matter.

15 So, I really do think the much more important  
16 issue is global safety, because that really speaks to what  
17 we should be saying to the physician and patient population  
18 who will use these drugs.

19 I see no evidence here for a global safety  
20 advantage. Perhaps neutrality is really shown, and I think  
21 given the number of events overall, the power here for  
22 global safety was actually pretty reasonable.

23 So, to me, there really isn't a proven global  
24 safety advantage.

25 DR. HARRIS: So, I think certainly with respect to

1 cardiovascular events, they are certainly neutral. Are  
2 there any other organs that were target organs that would  
3 make one feel that there was other than neutrality with  
4 respect to the comparators?

5 [No response.]

6 DR. HARRIS: Okay. I think I have consensus here  
7 that with respect to global safety, there does not appear to  
8 be a clinically meaningful safety advantage for Celebrex,  
9 and I believe that is the consensus that I have.

10 Let's move to Question No. 2. I am going to read  
11 it. In subjects taking low dose aspirin there was a reverse  
12 trend in results for both the complicated ulcer as well as  
13 combined complicated and symptomatic ulcer endpoints. Does  
14 there appear to be a safety signal in this database  
15 regarding concomitant use of COX-2 selective agents and  
16 aspirin?

17 I am going to start with our statisticians. Dr.  
18 Elashoff.

19 DR. ELASHOFF: It seems to me that a first step in  
20 addressing this question has to be one of looking within  
21 study, because there are some marked differences in the  
22 studies in terms of withdrawal rates, and so forth.

23 So, it seems to me that to look at this carefully  
24 requires some additional analyses which have not been done,  
25 which might make things look a little worse, might make

1 things look a little bit better, and that has to be part of  
2 understanding the answer to this.

3 DR. WILLIAMS: Since what we call specific COX-2  
4 inhibitors are really COX-1 spares, and aspirin is a COX-1  
5 inhibitor, I am not surprised that adding the two together  
6 deletes the effects of the COX-1 sparing, so I think that  
7 this does confirm what would be suspected. That is, that if  
8 you add aspirin, that that will defeat the benefits of  
9 isolated COX-2 inhibition.

10 DR. M. WOLFE: On the other hands, the effects are  
11 additive, and if you use addition NSAID, which is more non-  
12 COX-1 sparing, you may have additional problems although  
13 again it was shown in the study.

14 The other comment I was going to make was again to  
15 look at the aspirin situation. We can't treat people as if  
16 they are a joint or a heart, they are a person, and a person  
17 who needs cardiac prophylaxis, yet needs an NSAID, if we  
18 could demonstrate the NSAID was safer, they need to take the  
19 aspirin for the other purpose.

20 Now, one other thing I want to mention is that we  
21 are neglecting the fact, or it hasn't been mentioned yet,  
22 that if we do prevent GI bleeds, you are also indirectly  
23 preventing some myocardial infarctions to take place,  
24 because there are studies which show that about 1 in 7  
25 people who do have a GI bleed will have evidence by EKG or

1 enzymes or clinically of a myocardial infarction.

2 DR. SAMPSON: I just was reading the question  
3 again. It says in subjects taking low doses there was a  
4 reverse trend, and I think that is the issue, the safety  
5 signal. I was wondering if Dr. Goldkind or Dr. Witter might  
6 offer some sort of--to a statistician anyhow--some sort of  
7 clinical reason why this reverse trend might have taken  
8 place.

9 DR. GOLDKIND: Are you speaking to biological  
10 plausibility? I am aware of one article in the literature  
11 that studied COX-2 selective effects on the gastric mucosa,  
12 and then in combination with a nonselective agent, and the  
13 suggestion in that study, but it was not a study in humans,  
14 was that a combination of a COX-2 selective agent and a  
15 nonselective agent actually produced more damage than the  
16 nonselective agent alone.

17 I don't know if you are familiar with that. That  
18 is all I am aware of that would suggest some plausibility.  
19 It wasn't intuitive.

20 DR. CRYOR: I think you might be referring to John  
21 Wallace's study, who would have been one of our guests  
22 today, but unfortunately, is not here. I found this  
23 observation of interest. His animal study confirms or is  
24 consistent with this clinical observation that it requires  
25 both inhibition of COX-1 and COX-2 to confer this gastric

1 injury that we are observing in this combination with  
2 aspirin and celecoxib.

3 DR. DeLAP: I just wanted to add that I think we  
4 recognize that these kinds of preclinical studies with these  
5 kinds of drugs are oftentimes very problematic to do and to  
6 interpret, so I wouldn't want to give the impression that we  
7 are putting a lot of reliance on that.

8 DR. HARRIS: Well, if I may make a comment, we got  
9 distracted by that, the first statement some, but I think  
10 that helps us in terms of clarification.

11 DR. WITTER: I just wanted to answer because I was  
12 asked. The way that I was trying to approach it, or to help  
13 view the data, was in the context of this trial, so that we  
14 didn't have to go and kind of think about other trials and  
15 comparing other data bases, and that is why what I had tried  
16 to do was try to put this in some kind of context with what  
17 aspirin had done, not only with other GI events, but in  
18 other areas, as well, that that might help with some of the  
19 biologic plausibility or interpreting the data.

20 DR. GOLDKIND: Within the study itself, the  
21 relative rates, ibuprofen, which appeared to be the  
22 comparator where there was the strongest signal of  
23 inferiority, let's say, in terms of GI toxicity, ended up in  
24 those on aspirin to have actually less. The word "reversal"  
25 really referred to I guess the order of rates.

1 DR. SAMPSON: Just to follow up, again, just for  
2 my own clarification, the question is asking us to look at  
3 that 0.41 percent rate on aspirin, for ibuprofen, the  
4 reverse trend, does that provide a safety signal in the  
5 database, and I guess I don't know as a statistician what to  
6 make of that.

7 The 0.41 percent seems like a data anomaly rather  
8 than something that one would take and amplify, but I was  
9 hoping you might be able to shed some light on that for me.

10 DR. GOLDKIND: Well, I would just put that in  
11 conjunction with the symptomatic, as well as complicated  
12 ulcerates where it was a little above 3 percent versus 4 and  
13 5 percent range, I am not quoting exactly, but the trend was  
14 similar although, of course, the absolute rates were higher  
15 since it was a broader definition. Again the issue of  
16 whether it is simply an anomaly remains.

17 DR. WOFSY: I was just going to actually add one  
18 comment on the biologic plausibility discussion we were  
19 having, and I may require some correcting here, but we are  
20 talking about the addition of aspirin as if it now makes  
21 this COX-1 and COX-2 inhibition, and aspirin, at least in  
22 cardioprotective doses, may have a fairly effective effect  
23 on platelets, but it certainly isn't a potent cyclooxygenase  
24 inhibitor in that dose.

25 It is not my impression that it is, so I think we

1 need to be a little careful about saying, well, if you add  
2 81 mg of aspirin a day, you are blocking cyclooxygenase-1,  
3 so now you have got a nonselective effect.

4 DR. CRYOR: With respect to biologic plausibility,  
5 I differ in my opinion because we have looked at this, I  
6 have looked at this, and very, very low doses of aspirin are  
7 very potent in temperatures of gastric cyclooxygenase, at  
8 lower doses than were assessed in this clinical study that  
9 we are discussing today.

10 So, for me actually, there is biologic  
11 plausibility and evidence-based support for the  
12 observations.

13 DR. M. WOLFE: In addition, this study did not  
14 look necessarily at 81 mg only, it looked at less than 325,  
15 and relative risk in virtually every study at those dose is  
16 in the neighborhood of 2.3 to 2.6. Whether or not it is  
17 enteric coated makes no difference, so you have taken these  
18 patients, converted them to relative risk of aspirin  
19 minimally.

20 DR. WILLIAMS: Going back to a comment a long time  
21 ago, the comment I was trying to make that we have multiple  
22 choices for NSAIDs, and if we believe in the COX-2  
23 hypothesis, you may wish to choose one of the safer NSAIDs,  
24 but if that patient requires aspirin in cardioprotective  
25 doses, that negates any of the advantages those drugs have.

1 That is what I was trying to state before, not that I would  
2 withhold aspirin on somebody who was taking them to protect  
3 their stomach, but if they require aspirin, there is no  
4 longer an advantage to those drugs.

5 DR. M. WOLFE: I agree, but again, these effects  
6 are dose related, so does 325 more add to--was it 2.4 grams  
7 of ibuprofen? I don't know, and it is at higher dose, the  
8 more you add presumably, the higher the risk

9 DR. WITTER: Dr. Harris, if I might ask, maybe the  
10 sponsor might have this information, I don't, but I think  
11 low dose aspirin is not necessarily a low dose aspirin, and  
12 I don't know how the numbers came out in terms of the dosing  
13 in the particular groups, the three groups, I don't think we  
14 have time necessarily to get to that data today. Do you  
15 have that?

16 DR. GEIS: We do have that data, and we can show  
17 you that data.

18 DR. HARRIS: Specifically, that data.

19 DR. GEIS: Yes, we have that. Slide 411, please.

20 [Slide.]

21 DR. LEFKOWITH: We characterized aspirin use by  
22 dose in the study, and if you look at the usage of 81 mg  
23 versus 325 mg, and we have lumped together the very few  
24 number of users, 162 mg, with the 81 mg group, it splits  
25 roughly 50-50 in all the treatment arms.