

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

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

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

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

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

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

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

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

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

8 DR. HARRIS: Dr. Cryor.

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

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

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

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

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

4 DR. HARRIS: Dr. Sampson.

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

10 Celebrex treatments, one for Study 035 and one for Study  
11 102.

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

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

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

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

20 [Slide.]

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

1 pooled results.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

24 DR. M. WOLFE: Yes.

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

1 [Slide.]

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

10 DR. HARRIS: Any other questions?

11 [No response.]

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

14 [Break.]

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

18 **FDA Presentation**

19 **GI**

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

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

24 [Slide.]

25 First, I will briefly review some of the study

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

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

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

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

20           [Slide.]

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

23           [Slide.]

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

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

4 [Slide.]

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

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

13 [Slide.]

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

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

22 I will try and go through these briefly.

23 [Slide.]

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

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

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

13           [Slide.]

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

24           [Slide.]

25           Melena, hemoccult-positive stool, and fall in

1 hematocrit or hemoglobin. Hemoccult-positive stool and  
2 orthostasis or hemoccult-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 in 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 Cardiorenal-- 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.