

1 Again, much of this is a repeat of what has been
2 discussed. Organ-specific endpoints were defined although,
3 again, it was a large trial and meant to capture overall
4 safety as well as the organ-specific endpoints related to
5 the underlying physiologic hypothesis.

6 PUBs, perforations, symptomatic ulcers and
7 bleeding, was a primary hypothesis. Complicated PUBs, which
8 excluded those ulcers presenting with symptoms only, was a
9 second important study point. The statistical plan, again,
10 was to include a minimum of 120 confirmed PUBs, 40 confirmed
11 complicated PUBs and 6 months of enrollment following the
12 last patient randomized. The power calculation was produced
13 to detect a reduction in risk of at least 50 percent for the
14 primary GI hypothesis.

15 [Slide]

16 That hypothesis, as stated in the protocol, was
17 that the risk of confirmed PUBs during the treatment period
18 will be reduced in the group of patients with rheumatoid
19 arthritis taking 50 mg of Vioxx daily compared to the group
20 of patients with rheumatoid arthritis taking naproxen 1000
21 mg daily. Vioxx, administered at a dose of 50 mg daily,
22 will be safe and well tolerated.

23 [Slide]

24 The endpoints, to briefly review the definitions -
25 - any one of the following four clinical presentations would

1 be considered as a confirmed PUB: Ulcer, presenting with
2 signs or symptoms, or both, would require radiographic,
3 endoscopic or surgical confirmation. Perforation confirmed
4 radiographically, endoscopically, surgically or at autopsy.
5 Obstruction -- this required at least 24 hours of
6 postprandial nausea and vomiting in addition to evidence of
7 narrowing of the gastric outlet.

8 [Slide]

9 GI hemorrhage would require a healthcare provider
10 witnessed episode of frank hematemesis, coffee ground
11 emesis, NG aspiration of blood or coffee ground appearing
12 gastric contents, melena, to be distinguished from other
13 causes of dark stool, and active upper GI bleeding at the
14 time of endoscopy, surgery or angiography.

15 [Slide]

16 In addition, heme-positive stool associated with a
17 documented upper GI lesion, judged by the healthcare
18 provider to be the source of GI bleeding, associated with a
19 significant bleed or stigmata of recent bleed would also be
20 considered an event and, again, a drop in hemoglobin of 2
21 g/dL or more, hypotension or the need for transfusion were
22 required. These were rigorous definitions.

23 [Slide]

24 For a complicated event, any perforation and any
25 obstruction would be included in that category. A gastric

1 ulcer or duodenal ulcer, however, would only be included as
2 a complicated event if there was a sign of substantial,
3 potentially life-threatening associated. Again, this
4 excluded symptomatic ulcers.

5 [Slide]

6 To briefly review the results, these have been
7 shown previously, just formatted differently. Vioxx
8 compared to naproxen, the rate, either per 100 patient years
9 or cumulative rate, did show a risk reduction, 0.46, with a
10 highly statistical significant p value.

11 [Slide]

12 Complicated PUBs, again Vioxx compared to
13 naproxen, showed a relative risk of 0.43, and these are the
14 differences seen per 100 patient years as well as the
15 cumulative rates. Not surprisingly, the cumulative rates,
16 the absolute numbers are substantially less for complicated
17 PUBs which was a more rigorously defined and rare endpoint,
18 fortunately, than the simple PUBs.

19 [Slide]

20 Again, just to look at the types of confirmed
21 PUBs, it was what one would expect looking at the
22 literature. The majority were symptomatic ulcers, gastric
23 and duodenal. A subset of these were upper GI bleeds, and
24 perforations and obstructions were rare in the database.

25 [Slide]

1 Now moving on to subgroup analysis based on risk
2 factor, looking at a prior history of PUB, as has been
3 presented, the risk reduction is maintained across both risk
4 categories. The point that I would like to make in this
5 slide is that while the risk reduction is substantial and
6 persists in the high risk group, the absolute rates, either
7 per 100 patient years or accrued rate in this slide, here,
8 is of note even in the Vioxx group. So that, while the
9 relative risk in that population goes down, the absolute
10 risk is actually quite significant and, compared to a lower
11 risk population even on naproxen, again remains a
12 significant event rate.

13 [Slide]

14 Looking at age as a risk factor, again the
15 relative risk reduction is maintained both for the
16 population under 65 and the population over 65 but, once
17 again, the high risk group does continue to have absolute
18 rate of events that are similar to the rate seen in the
19 naproxen group in the lower risk population.

20 [Slide]

21 This slide will look familiar to a lot of people.
22 If age and a history of PUB are independent risk factors for
23 ulcer disease, then the findings of a high risk in
24 association with therapy may simply represent the intrinsic
25 risk associated with that population rather than any

1 additive effect of the drug. So, there may be no causality
2 between the drug and the added risk. On the other hand,
3 there may well be an interaction between the underlying risk
4 population and the drug such as to produce an exaggerated or
5 a higher attributable risk to therapy.

6 [Slide]

7 So, the outstanding question related to the
8 absolute rates of events that we saw in the previous slides
9 is whether high risk patients should be treated with lower
10 relative GI risk NSAIDs, or does the overall residual or
11 absolute risk associated with usage continue to represent a
12 contraindication for these patients? The answer to that, of
13 course, involved clinical information related to the
14 individual patient and the strength of the indication for
15 treatment, and this question has obvious usage implications.

16 [Slide]

17 GI risk, again, in special populations -- other
18 outstanding questions are the GI risk of co-administration
19 of aspirin and Vioxx where further data is needed, the GI
20 risk of co-administration of aspirin and Vioxx in the
21 elderly where more information is needed, and the
22 subpopulation of both elderly and a history of PUB -- what
23 the GI risk in that population would be. Even this large
24 database couldn't answer that question because of how small
25 the intersection of elderly and history of PUB would be in

1 terms of the numbers of patients enrolled.

2 [Slide]

3 In terms of the generalizability of GI safety, as
4 the sponsor has noted, Vioxx did have a substantial decrease
5 in risk for the PUBs and complicated PUBs, as noted here.

6 In terms of the degree of absolute risk, a comparative
7 database cannot answer that. Again, the issue of relative
8 risk compared to other NSAIDs has been addressed to some
9 extent by the sponsor although further data is needed.

10 [Slide]

11 I will briefly review the data that was presented
12 from the IIb and III studies, which was a meta-analysis of
13 PUBs using Vioxx at all three doses as one group versus
14 NSAIDs as a composite group. It is important to note that
15 three doses of Vioxx were used in this meta-analysis, 12.5,
16 25 as well as 50 mg, and although there was a third
17 comparator, nabumetone, in the database the exposure was
18 very small, and the next slide will only show ibuprofen and
19 diclofenac where there was meaningful exposure. It is also
20 important to note that there was a large spread of exposure
21 through this meta-analysis, with some studies and
22 comparators only having exposure to 12 weeks, while some
23 doses of Vioxx and some comparators had exposure all the way
24 out to 52 weeks.

25 [Slide]

1 This slide breaks down the number of patients
2 enrolled for each dose and comparator, and the duration for
3 which there is some data available. As you can see, the
4 majority of exposure for Vioxx was at the two currently
5 approved chronic doses, with a much smaller database at the
6 dose used in the VIGOR trial. Again, the duration was much
7 longer at these lower dosages compared to the higher dose
8 for studies in the original NDA.

9 Ibuprofen, similar exposure in terms of numbers
10 enrolled to Vioxx, 50 mg and, again, a fairly short-term
11 exposure. Diclofenac did have a slightly larger number of
12 patients enrolled in studies IIb and III and had a longer-
13 term exposure. This asterisk applies also to the next
14 slide. The only data points plotted are those for which
15 there were 200 patients present at the end of the interval.

16 [Slide]

17 One caveat in looking at this is that confidence
18 intervals are not here. If they were, there would be huge
19 overlap because the number of events in this database was
20 quite small. But, when trying to analyze a meta-analysis,
21 we think it is important to look at the data that is there
22 before combining to see how appropriate it is to combine and
23 what trends are being enhanced and what trends are being
24 diminished by combining studies.

25 This line, here, represents the ibuprofen group.

1 Exposure only extends out to 12 weeks for 200 or more
2 patients, and this is the cumulative PUB rate. As you can
3 see, this has the highest of all of the comparators across
4 these studies. The Vioxx 50 mg is shown here. Again,
5 exposure of 200 patients or more ends at 12 weeks in that
6 database. The other three comparators, the Vioxx 12.5 mg,
7 25 mg, as well as the diclofenac are all shown here. They
8 all three do have more significant exposure in terms of
9 duration, and there is overlap with diclofenac between the
10 two doses and only towards the end, again, these three data
11 points can probably be looked at as overlapping as, in fact,
12 with the confidence interval one may see across the entire
13 table.

14 [Slide]

15 Conclusion of the review of the meta-analysis of
16 Phase IIb/III studies, the Vioxx dose and duration of
17 exposure do affect the associated rates. The ibuprofen and
18 diclofenac did not perform similarly in that database.
19 NSAIDs as a composite comparator may not be appropriate and,
20 in a general sense, meta-analyses combining heterogeneous
21 groups may be problematic.

22 [Slide]

23 Overall conclusions, Vioxx 50 mg was associated
24 with a lower rate of PUBs and complicated PUBs compared to
25 naproxen 1000 mg in patients with rheumatoid arthritis not

1 requiring low dose aspirin. Risk reduction did extend
2 across all high risk groups.

3 [Slide]

4 High risk groups, specifically the elderly and
5 those with a history of prior PUB continue to have
6 significant absolute risk of PUBs that was seen in this
7 range for accrued rate. The generalizability of risk
8 reduction to patients requiring low dose aspirin has not
9 been evaluated. Generalizability to other NSAIDs, all
10 traditional NSAIDs, remains a question. Thank you.

11 **Cardiovascular Review**

12 DR. TARGUM: Good morning.

13 [Slide]

14 I am Dr. Shari Targum. I am a cardiologist and
15 medical officer in the Division of Cardioresenal Drug
16 Products, and I am here this morning to present the
17 cardiovascular safety data from the VIGOR study.

18 [Slide]

19 You have already heard some of this. I will
20 briefly summarize the key features in the VIGOR trial. It
21 was a large, comparative study with a nine-month median
22 follow-up. There was no placebo arm, and the primary
23 endpoint was GI in nature.

24 [Slide]

25 In terms of baseline demographics for this study

1 population, it was mostly female, mostly under 65. A
2 majority were Caucasian, and about half had any cardiac risk
3 factor.

4 [Slide]

5 It should be noted that the two groups were evenly
6 matched for hypertension, diabetes, current smokers,
7 hypercholesterolemia and past atherosclerotic disease, which
8 was less than 6 percent. We have no information on
9 inflammatory markers, as was already mentioned.

10 [Slide]

11 Exclusions from VIGOR -- patients were excluded if
12 they had angina or congestive heart failure with symptoms
13 that occur at rest or minimal activity. If they had
14 uncontrolled hypertension, and here it was defined; stroke
15 or transient ischemic attack within the previous two years.

16 [Slide]

17 Other exclusions from VIGOR included patients
18 taking aspirin, even low dose aspirin, or other anti-
19 platelet agents, and patients requiring warfarin or heparin.

20 [Slide]

21 There was a note that patients with a history of
22 myocardial infarctions or coronary arterial bypass grafting
23 more than one year prior to study might participate if they
24 did not require any of the excluded concomitant medications.

25 [Slide]

1 I would like to talk a little about the vascular
2 events adjudication committee. This was a blinded, external
3 vascular event committee comprised of three separate sub-
4 specialty committees for cardiac, cerebrovascular and
5 peripheral vascular events respectively, and there existed
6 prespecified criteria for defining vascular events such as
7 MI, etc.

8 [Slide]

9 This is taken from the procedures for
10 adjudication. It is worth noting that the vascular events
11 of primary interest for analysis -- these were prospectively
12 defined events as opposed to the APTC endpoints, which have
13 been discussed, which were post hoc. So, it is worth
14 mentioning that.

15 The vascular events for analysis were split into
16 primary interest and secondary interest. The ones of
17 primary interest included myocardial infarction, unstable
18 angina, ischemic stroke, acute arterial thromboembolism and
19 sudden death or resuscitated cardiac arrest.

20 [Slide]

21 There were also noted vascular events of secondary
22 interest, including pulmonary embolism, venous thrombosis,
23 non-fatal cardiac thrombosis and transient ischemic attack.
24 According to the sponsor, the definition of confirmed
25 thrombotic events is a composite of these vascular events of

1 primary and secondary interest.

2 [Slide]

3 This slide is a time-to-event plot. On the Y axis
4 is cumulative incidence and on the X axis is months of
5 follow-up. The events that I previously defined for you are
6 here. The top curve is rofecoxib; the bottom curve is
7 naproxen. You can see that the two groups are different.
8 In fact, they are significantly different.

9 [Slide]

10 Points to consider -- there are no prospective
11 randomized, placebo-controlled trials to support a
12 cardiovascular benefit for naproxen. In addition, it is not
13 known that rofecoxib is worse than placebo

14 [Slide]

15 In conclusion, regardless of mechanism, with
16 cardiovascular benefit with naproxen or cardiovascular risk
17 with rofecoxib, the cardiovascular data favor naproxen.
18 Thank you.

19 **Statistical Review**

20 DR. LI: Good morning.

21 [Slide]

22 My name is Qian Li, a statistical reviewer from
23 the Office of Biostatistics. I am going to discuss the
24 meta-analysis for cardiovascular risk assessment for
25 rofecoxib.

1 [Slide]

2 To begin with, let's first look at the cumulative
3 incidence curves of thrombotic cardiovascular events
4 observed in the VIGOR trial for rofecoxib 50 mg and
5 naproxen. You have seen this curve before in Dr. Targum's
6 presentation. The difference for cardiovascular events
7 between the two treatment groups was statistically
8 significant. Rofecoxib 50 mg actually doubled the risk of a
9 thrombotic cardiovascular event in naproxen. Notice that the
10 two curves start to diverge at six weeks after the
11 treatment, and are further separated after the treatment.
12 This suggests that the risk ratio is not constant over time.

13 [Slide]

14 To further understand the risk of cardiovascular
15 events associated with rofecoxib 50 mg, the sponsor
16 conducted a meta-analysis which consisted of 25 studies and
17 more than 28,000 patients. The key features of the meta-
18 analysis are that different dose levels of rofecoxib were
19 put together, from 12.5 mg to 50 mg. Studies of different
20 durations were put together, with a duration from six weeks
21 to more than one year. And, the different indications were
22 put together by stratified analysis. Those indications
23 include rheumatoid arthritis, osteoarthritis and Alzheimer's
24 and back pain.

25 [Slide]

1 The issues we have about the meta-analysis focus
2 on rofecoxib 50 mg. The question we have is whether the
3 meta-analysis can adequately address the role of rofecoxib
4 50 mg in relation to cardiovascular events.

5 [Slide]

6 Let's first look at the meta-analysis data sets.
7 Of the 28,000 patients in the meta-analysis data sets, there
8 are about 6000 patients on rofecoxib 50 mg. Of the 6000
9 rofecoxib 50 mg patients, 4,047 patients were from the VIGOR
10 trial, which is a long-term study, more than six months.
11 Also, in the VIGOR trial there were about 1900 patients on
12 rofecoxib 50 mg and about half of those 1900 patients are
13 from a study that has a duration longer than six months. As
14 you can see, there are not many patients in rofecoxib 50 mg
15 outside VIGOR in this meta-analysis data set, especially for
16 study duration longer than six months.

17 [Slide]

18 In addition, we have some concerns about the meta-
19 analysis. One, the risk ratio between rofecoxib and the
20 comparator may not be constant over time. This was observed
21 in the VIGOR trial and the treatment difference started to
22 show around six weeks after the treatment. So, a short-term
23 study may not be able to demonstrate the treatment
24 difference. We need long-term exposure data with a
25 sufficient number of patients.

1 [Slide]

2 Another concern is that the risk may not be the
3 same for different dose levels of rofecoxib. It is common
4 sense that pooling may obscure the risk associated with the
5 high dose group. This is not a conceptual concern.

6 [Slide]

7 In fact, there are data to suggest a trend of
8 increased risk with rofecoxib 50 mg. This data, shown in
9 this slide, was provided by the sponsor on request of the
10 agency for studies with a duration of at least six months or
11 longer. As you can see, 50 mg appears to have a higher
12 relative risk ratio in comparison to both naproxen and other
13 NSAIDs, including ibuprofen and diclofenac. This slide is
14 not to show that there is a dose response, but not to deny
15 the higher risk of 50 mg rofecoxib.

16 [Slide]

17 To summarize the major limitation, pooling
18 different dose levels is problematic for evaluation of
19 rofecoxib 50 mg. This makes the meta-analysis invalid to
20 assess the risk of rofecoxib 50 mg. Furthermore, there is
21 not enough data in the meta-analysis data sets that has
22 rofecoxib 50 mg outside the VIGOR trial, especially for a
23 duration longer than six months.

24 [Slide]

25 In conclusion, the meta-analysis doesn't resolve

1 the role of rofecoxib 50 mg in relation to the risk of
2 cardiovascular events observed in the VIGOR trial. Thank
3 you.

4 **Summary**

5 DR. VILLALBA: In the second part of my
6 presentation I want to go over several important issues.

7 [Slide]

8 I will cover the general safety in the VIGOR
9 study, then talk about cardiovascular safety. Actually,
10 this is not the last set of slides I have because I have
11 changed the title of this subsection and I will explain why
12 later. Then I will talk about risk/benefit assessment and
13 co-use of aspirin, postmarketing safety and the conclusions.

14 [Slide]

15 Evaluation of general safety in the VIGOR study
16 was done by looking at routine safety parameters, such as
17 death, serious clinical adverse events, dropouts, lab
18 adverse events. These were prespecified in the protocol,
19 and we requested that an additional analysis of number of
20 hospitalizations. There were also prespecified analyses of
21 NSAID-related events that I mentioned earlier.

22 [Slide]

23 This is the table of deaths in the VIGOR study.
24 As you can see, the number was small and it was similar in
25 percentage, a little higher in the rofecoxib group but too

1 small to make any meaningful statistical comparisons. The
2 most common cause of death was cardiovascular in both
3 groups, and I just want to point out two cases of death
4 related to GI bleeding in the rofecoxib group and one case
5 in the naproxen group. Regarding the patient with hepatic
6 necrosis on naproxen, this happened after the end of the
7 treatment but it could have happened during treatment. But
8 the important issue is that this patient was concomitant
9 methotrexate, therefore, this cannot be attributed only to
10 naproxen.

11 [Slide]

12 I will go through slides with the safety
13 endpoints, and I don't want to spend too much time on each
14 slide. The general point that I want to make is that GI
15 safety favored rofecoxib clearly and consistently. However,
16 the overall safety was in favor of naproxen. There was an
17 equal number of events, all higher in the rofecoxib group as
18 compared to the naproxen group. Here we have serious
19 adverse events with an incidence of more than one percent.

20 [Slide]

21 Here we have dropouts due to adverse events.
22 Again, the number is similar but if you go by category the
23 number of cardiovascular events specifically is higher in
24 rofecoxib than in naproxen, and that makes the total number
25 similar.

sg

1 [Slide]

2 This is the number of hospitalizations, which is
3 consistent with the serious events. We thought this group
4 would give us a more clear idea of how many patients really
5 required hospitalization.

6 [Slide]

7 Regarding laboratory adverse events, the number
8 was higher in rofecoxib as compared to naproxen. There were
9 22 dropouts due to laboratory AEs in the rofecoxib group as
10 compared to 12 on naproxen. There were three serious
11 hematologic events, leucopenia and one case of aplastic
12 anemia in a patient who died of pneumonia complicating
13 aplastic anemia. The three patients were on methotrexate.

14 [Slide]

15 This is the list of prespecified NSAID-related
16 adverse events and CHF. The sponsor has already shown this
17 slide but not with the p values. Actually, the p values are
18 kind of irrelevant in that when we look at safety we don't
19 look for statistical significance differences; we look for
20 trends. But, in any case, for GI and for hypertension there
21 was a statistically significant difference in favor of
22 rofecoxib. Then, we have edema-related, liver-related with
23 trends in favor of naproxen, and for renal there was a
24 similar number of dropouts.

25 [Slide]

1 In summary, the GI safety favored rofecoxib but
2 overall the general safety parameters trended in favor of
3 naproxen, particularly due to the excess in serious
4 cardiovascular events in the rofecoxib group.

5 [Slide]

6 I am going to talk now about cardiovascular safety
7 and, as I mentioned, I changed this part because I had
8 included several slides about studies using aspirin in
9 cardiovascular prophylactic trials and then I decided to
10 take them out because there are many cardiologists here that
11 I hope will address that issue.

12 [Slide]

13 This is the time-to-event plot again. I apologize
14 because it doesn't read very well but that was the table
15 provided by the sponsor and we cut and pasted from the
16 submission to make this slide. But I want to make several
17 points here. I know it was shown by two reviewers earlier.
18 On the Y axis we have the cumulative incidence of events and
19 on the X axis we have the follow-up in months. What is very
20 important here is the number of patients at each time point.
21 You cannot read it well but there are 4000 patients per arm
22 at the beginning, approximately 3000 patients at 8 months,
23 and then the curve is cut when there were 500 patients
24 approximately in each arm.

25 As we mentioned before, the separation starts at

1 six weeks and is maximal after eight months, and we don't
2 know what happened after ten months. This trial was
3 appropriate with a long follow-up for looking at GI events,
4 but probably not long enough for looking at cardiovascular
5 events. Here, as you can see, the relative risk of
6 developing serious cardiovascular events in VIGOR was 2.37,
7 so a little more than twice.

8 [Slide]

9 Here I included the definitions, and you were
10 already primed to these definitions so I don't need to spend
11 too much time on that but they were really confusing to me
12 when I did the review. So, I thought it was nice to put a
13 slide together. The endpoints that the study used, the
14 predefined endpoints were the adjudicated, confirmed serious
15 cardiovascular events, confirmed by the case review
16 committees. This was prespecified in a standard operations
17 procedure that had been written long before the VIGOR trial
18 was even started because it was planned to be used in all
19 trials of rofecoxib. But this was really after the Phase
20 IIb/III trials were completed.

21 The APTC is the composite endpoints of cardiac
22 death, non-fatal MI and stroke, and this includes
23 hemorrhagic stroke and excludes peripheral events, and also
24 excludes unstable angina and TIAs.

25 [Slide]

1 Here is the list of events that were included for
2 analysis.

3 [Slide]

4 This is just to show you how the same events can
5 be seen in different ways if you look at the investigator
6 reported events, adjudicated events or APTC composite
7 endpoints. In any case, there is consistency and rofecoxib
8 has the higher risk, almost twice or more than twice in the
9 three ways of looking at these events. But, as you can see,
10 the number of events with the APTC composite is smaller than
11 looking in the other ways. In any case, this is the way it
12 was prespecified. The APTC was post hoc but it is a way
13 that is widely accepted in anti-platelet trials, and I think
14 that understanding this difference will allow us to try to
15 compare this with other published data that I hope some
16 cardiologists will discuss.

17 [Slide]

18 This is the data. Now, what are the hypotheses?
19 One hypothesis is that this is the prothrombotic effect of
20 rofecoxib, and we do have the biological plausibility to
21 backup this hypothesis. If this is true, is this related to
22 the 50 mg dose? Is it related to the exposure? Or, is it
23 related to the disease? We don't know. Is this a
24 cardioprotective effect of naproxen? The sponsor has put
25 together a very strong argument in favor of this hypothesis

1 and there is also biological plausibility to explain that.
2 But, it could be that none of these are the factors, that
3 there is some other unknown factor. So, I just want to
4 point out that if we are going to accept the
5 cardioprotective effect of naproxen, this is a very
6 impressive cardioprotective effect.

7 We have a median follow-up of nine months in a
8 population with no medical indication for cardiovascular
9 prophylaxis in a relatively small size because all the
10 cardiovascular preventive trials include large numbers of
11 patients followed for several years. Therefore, it is not
12 very convincing to us that this is the whole explanation,
13 and there are no controlled studies of naproxen versus
14 placebo for cardiovascular prophylaxis. There are some
15 available placebo-controlled studies with aspirin and I
16 would really challenge the cardiologists here to explain to
17 me how this correlates with what we know from those data.

18 [Slide]

19 The sponsor performed a meta-analysis with 28,000
20 patients to try to demonstrate that there was no evidence of
21 prothrombotic effect in the whole database for rofecoxib,
22 however, there are important limitations to that meta-
23 analysis and, as Dr. Li already discussed, the studies were
24 of different lengths, from 4 weeks to 86 weeks, and most
25 patients were exposed for less than 6 months. You remember

1 from the time-to-event curve, before 6 months you are not
2 going to see much. Therefore, we would like to see what
3 happened after 6 months or even after a year.

4 the study also included different doses, 12.5, 25
5 and 50, and most patients were exposed to the 25 mg dose or
6 less. There were multiple comparators which may be
7 associated with different risks of cardiovascular events,
8 and there were different diseases that may be associated
9 with different risks of cardiovascular events.

10 [Slide]

11 Out of the 28,000 patients only 600 -- and I think
12 that this number is different from what Dr. Li presented
13 but, anyway, less than 1000 patients were exposed to 50 mg a
14 day for at least 6 months in studies other than VIGOR. So,
15 I don't think that this meta-analysis can answer the
16 question raised in a randomized, controlled study, large
17 study with one dose with a 9-month follow-up.

18 [Slide]

19 In summary, regarding cardiovascular safety the
20 VIGOR study favored naproxen. In cardiovascular thrombotic
21 events for hypertension, CHF or hypertension, fluid
22 retention and edema we had a signal in the NDA and this is
23 dose dependent. However, for cardiovascular events we don't
24 have a good explanation. The original NDA had a small
25 database. The sponsor's meta-analysis has serious

1 methodological limitations to answer the question.

2 I did not include in the slide the Alzheimer's
3 studies, and I have not reviewed those studies, but the
4 number of patients included in those studies was less than
5 1000 patients per arm, the two of them together. Therefore,
6 these studies were not powered to show any difference with
7 placebo. I will not make any conclusions about those
8 placebo studies in Alzheimer's disease. Also, the dose that
9 was used in that study was 25 mg, not 50 mg.

10 [Slide]

11 Now, regarding risk-benefit assessment and co-use
12 with aspirin, we know that a large part of the patients with
13 arthritis will probably qualify for cardiovascular
14 prophylaxis. Patients with increased risk of certain
15 cardiovascular thrombotic events should be on concomitant
16 aspirin. However, the effect of concomitant use of
17 rofecoxib with low dose aspirin on GI and cardiovascular
18 risk is unknown. The sponsor had conducted, I think, five
19 studies that allowed aspirin from the start. Three of those
20 five studies were study 85, 90 and 58. These studies were
21 6-week studies and looked at the 12.5 mg dose. Therefore,
22 those cannot really address the issue.

23 And, there was a rheumatoid arthritis study that I
24 didn't have the opportunity to review, and I think this is
25 in one of the Phase III studies for efficacy in rheumatoid

1 arthritis, and the only one that had a large number,
2 although it was kind of short for what we are looking for,
3 was study 102, the ADVANTAGE study. This was a 5500 patient
4 database to look at rofecoxib 25 mg versus naproxen 1000 mg
5 a day, and this population was allowed to use aspirin and
6 approximately 12 percent was using low dose aspirin.

7 These are the results. This is just preliminary
8 data. So, I don't want to make any interpretation. But,
9 you see that the events seem to go in the same direction.
10 Again, this is 25 mg and it is only 12 weeks, and it was a
11 different population because these were patients with
12 osteoarthritis.

13 [Slide]

14 In summary, there is not much data on concomitant
15 use of aspirin.

16 [Slide]

17 Regarding postmarketing, I have one slide just to
18 mention that we have received reports of NSAID-related
19 events -- GI, renal, liver, anaphylactoid reactions,
20 prothrombin time prolongation with coumadin co-use. So, the
21 safety profile looks like other NSAIDs. And we have
22 received reports of serious GI events and even deaths in
23 postmarketing.

24 [Slide]

25 In conclusion, successfully VIGOR showed that

1 rofecoxib was superior to naproxen, and only naproxen, not
2 other NSAIDs, in a population of patients not taking
3 aspirin. Overall, there was no safety superiority of
4 rofecoxib over naproxen, mainly due to an excess of serious
5 cardiovascular events in the rofecoxib group compared to the
6 naproxen group. Rofecoxib 50 mg is not the dose approved
7 for chronic use; 12.5 and 25 are the doses approved for
8 chronic use. Although 50 mg is approved for treatment of
9 acute pain, the chronic use of this dose is not recommended.

10 [Slide]

11 Postmarketing safety raises the issue that serious
12 GI events are still present, particularly in high risk
13 populations. And, we ended with important questions. Is
14 there a prothrombotic effect of rofecoxib? And, what would
15 be the impact of chronic co-use of low dose aspirin in GI
16 and cardiovascular events? That is my last slide.

17 DR. HARRIS: Thank you, Dr. Villalba. I am going
18 to ask members of the committee if there are any questions
19 they have related just to clarification of any of the data
20 that was presented by the FDA. I will go left to right this
21 time. Yes?

22 DR. WOFSY: Thank you. Two of the presentations,
23 Dr. Villalba and Dr. Goldkind, commented on serious GI
24 complications. Dr. Goldkind pointed out that in high risk
25 patients there are serious GI complications that occur in

1 patients on rofecoxib, and, Dr. Villalba, you pointed out
2 that in postmarketing there were serious GI complications.
3 There are also serious GI events in people who don't take
4 these drugs, and people who take penicillin, and people who
5 take anything. Do you have any data to bring to bear on
6 whether there is more of this than you would expect? What
7 does it mean, in other words, that we see this? We see this
8 in every conceivable population.

9 DR. GOLDKIND: Yes, I think what you are looking
10 for is an absolute underlying risk of events, and there are
11 databases that address that. I think yesterday there were
12 some slides that spoke to that issue. The problem is
13 comparing across databases is difficult. Just the time
14 element, looking historically, at a database is difficult
15 because the definitions used to define an event in one study
16 may be hospitalization, in another it may be death, in
17 another it may be a symptomatic ulcer. So, the definitions
18 are different, and how well you ascertain those events
19 changes over time. A patient with an ulcer now, even if
20 they have an episode of hematemesis, may be endoscoped as an
21 outpatient and if there is no high risk findings at
22 endoscopy or where the doctor is confident there won't be
23 rebleed, you may not even hospitalize. Whereas, in an
24 earlier database that person would have been not only a PUB
25 or a POB but would have been considered an even more serious

1 event. So, I don't think there is a good answer to the
2 question of how many of the events or what percentage of the
3 events that we see in the rofecoxib group are related to
4 underlying risk factors and, in fact, are not attributable
5 to the drug.

6 DR. WOFSY: I take your answer I think to be as
7 clear as it can be but, in effect, I am asking what point
8 are you trying to make by giving us this information.

9 DR. GOLDKIND: In the high risk group or in
10 general?

11 DR. WOFSY: Either. By giving us the information
12 that in postmarketing experiences or in high risk patients
13 GI events happen, what is the point?

14 DR. GOLDKIND: I think it is important to know. I
15 mean, there are limitations of postmarketing data. If there
16 are 13 million prescriptions, you know, you could have a
17 list that would extend through the entire PDR if you were
18 going to list anything ever reported. Actually, I will let
19 Dr. Villalba respond to that since that was her point.

20 In terms of the issue of relative risk, I think it
21 is very important. Again, you can look at the same data and
22 say because of the advantage, the relative risk reduction,
23 this is precisely the drug to use, or you can say the
24 underlying -- the absolute risk, I should say, not the
25 underlying is high enough -- how much is drug; how much is

1 disease we don't know, but if it is high enough there then
2 you reassess, in a sense I guess, the drug category or the
3 whole treatment modality as NSAID versus another modality
4 altogether. That, obviously, relates to the strength of the
5 indication. As I said in my discussion, if you have strong
6 indication for a category of drug and you need the
7 pharmacodynamic properties, then you obviously choose that
8 one that appears safer.

9 DR. VILLALBA: My answer would be that we have a
10 label that has a GI warning for non-steroidals and, based on
11 this study, the sponsor is proposing to downgrade that label
12 and move it to the precautions section, and be different
13 from the other NSAIDs, and I think that the fact that we
14 still have reports in postmarketing of these kinds of events
15 supports the fact that we shouldn't be changing -- well, I
16 mean modifying the label, yes, but a dramatic change in the
17 label, I think that is not warranted.

18 DR. HARRIS: Can I take the chair's prerogative
19 and just ask a question myself, if I might? Is there a
20 stage in the postmarketing surveillance where one says that
21 we have seen something often enough that, you know, there is
22 an alert? I mean, there are alerts and, you know, can one
23 get a sense of that her?

24 DR. VILLALBA: I am glad that the reviewer from
25 postmarketing is here, so could someone answer that

1 question?

2 DR. BRINKER: Hi. My name is Allen Brinker and I
3 am a medical epidemiologist and one of a group of people
4 from postmarketing that helps review these drugs. As far as
5 your question goes, there is no threshold for an absolute
6 signal. The safety evaluators and the medical officers that
7 are involved with this drug all review these case reports,
8 these spontaneous case reports that bubble up from an
9 unknown number of patients that are exposed to these drugs.
10 It doesn't take very many cases of fulminant liver failure
11 in otherwise healthy people for us to get very interested in
12 drug safety. If we see a lower threshold of events, GI
13 events or cardiovascular events that float up from a
14 population at risk, it is much harder to make a signal out
15 of that. Does that help you?

16 DR. HARRIS: Yes, I think it does. Dr. Wolfe, you
17 had your hand up first so I am going to give you a chance.

18 DR. WOLFE: I want to actually address this issue
19 because the question was asked is there a background
20 prevalence of GI bleeding and the answer is yes. I think
21 that has to be very carefully considered when you talk about
22 a post hoc analysis because a person who has, for example,
23 *H. pylori* infection and has a bleed, if they are taking
24 NSAIDs who knows what caused the bleed in that situation. I
25 don't think any claims were made here by anybody that you

1 are decreasing the risk to zero. There is still going to be
2 a background level and, actually, the older one gets, as we
3 have seen, the higher the prevalence rate.

4 DR. PINA: A question for Dr. Villalba. In study
5 102 I noted that the slide that you showed had ischemic CVAs
6 of six versus zero against naproxen. Aspirin was allowed in
7 the trial. Were any of those patients, indeed, on or off
8 aspirin? Do we know that?

9 DR. VILLALBA: Actually, this is just preliminary
10 data. I have not reviewed this study. A complete report
11 has not been submitted to the agency and these preliminary
12 data were submitted because we requested it. This is the
13 last database. We want to know what is going on. But the
14 sponsor could answer that question.

15 DR. HARRIS: Please.

16 DR. REICIN: Can you hear me because the mike
17 isn't on? The five strokes occurred in non-aspirin users.

18 DR. HARRIS: Dr. Cryer?

19 DR. CRYER: I would just like to follow up to Dr.
20 Wolfe's response about this background rate that was seen in
21 the postmarketing experience. I addressed the same question
22 that you did with respect to the postmarketing experience on
23 GI bleeds with rofecoxib. According to my assessment of
24 what I read in our briefing documents, it appears that the
25 rate of complications that have been experienced with

1 rofecoxib are actually less than would have been expected
2 given the background rate in individuals not on NSAIDs.

3 DR. HARRIS: There is just one other question I
4 have to ask, and this is talking about bubbling to the
5 surface. There seemed to be some comment in the
6 postmarketing surveillance about early renal events. In
7 fact, the thinking was that it occurred later but it seemed
8 as if with, I think, both of the COX-2 inhibitors there were
9 some of these events that were reported that occurred
10 earlier than one might anticipate. Now, we are not sure
11 whether it is the drug, not the drug, or something. Is this
12 one of the things that perhaps might bubble to the surface?

13 DR. VILLALBA: I would ask again the reviewer from
14 postmarketing, if you want to answer that question.

15 DR. BRINKER: Were you directing this comment
16 towards postmarketing or towards our interpretation of the
17 VIGOR trial?

18 DR. HARRIS: Postmarketing entirely, and this was
19 again from reading some of the background data and I think
20 there was a comment made about some renal events occurring
21 early after taking these drugs and apparently the labeling
22 indicated otherwise.

23 DR. BRINKER: Indeed, we have data on that.
24 Getting back to what spontaneous reports data are all about,
25 and they are really designed for the qualitative detection

1 of a serious, rare and unexpected event. We can present
2 data from these case reports that we have received on this
3 issue if you want a qualitative description of some of these
4 cases that have come in.

5 I will also take this question back to the people
6 who have looked at the VIGOR trial and see if they want to
7 comment on anything that they saw in the setting for a
8 quantitative description of risk in a randomized, controlled
9 trial.

10 DR. VILLALBA: As I mentioned regarding renal
11 events, there was no difference in dropouts due to renal-
12 related events as per the sponsor numbers. There were more
13 renal events in the rofecoxib group but there was not a
14 large difference between the two of them.

15 DR. HARRIS: Thank you. Dr. Nissen?

16 DR. NISSEN: Several reviewers commented on this
17 apparent inflection point in the cardiovascular event data
18 from eight months on. I wonder about how much confidence
19 the reviewers have that that is a real phenomenon as opposed
20 to just sort of an anomaly of the statistics of all of this.
21 Is it consistent across groups? Was it seen, for example,
22 in the Phase IIb/III data from the sponsor? What do we know
23 about this? Is that a real phenomenon? How certain are we
24 of that?

25 DR. VILLALBA: Well, the Phase IIb/III was a

sg

1 smaller database and the doses were all kind of doses, and
2 the number of patients exposed to any dose for more than six
3 months was limited. Therefore, I don't think that we can
4 compare the two databases but it may be related to the
5 number of patients at that point. There were close to 1000
6 patients at eight months.

7 DR. HARRIS: I think you are referring to that
8 apparent sharp increase after eight months, and I am pretty
9 sure the sponsor gave a response to that, and I would like
10 you to repeat it.

11 DR. ZEGER: Hello. I am Scott Zeger. I am a
12 professor of biostatistics at Johns Hopkins University, and
13 I had a chance to review these data and also noticed that
14 inflection point and thought some about it. I asked Merck
15 to do some investigations about it, and there is no
16 statistical significance to that inflection point based upon
17 their looking for a change in the relative risk over time.

18 But I also got the data myself and did some
19 analyses, and I cut it as many ways as I knew how and there
20 is really no evidence that there is a meaningful change
21 there. In fact, if you just think about it for a second and
22 take the last 20 events, which is from month 9 on, and there
23 is a relative risk of about 2.3 over the whole period of
24 time, and you say how should the 20 events split, and they
25 should split with a 2.3 relative risk of about 14 to 6 --

1 that is how they should split if there is no change. What
2 we saw was 16 to 4. So, it was 2 events difference than
3 what you would expect overall.

4 I noticed the shape as well and I looked into it
5 quite carefully, and there is really no evidence -- no
6 statistical evidence to lead us to conclude that there has
7 been a change there.

8 DR. NISSEN: That answers my question.

9 DR. HARRIS: Dr. Pina?

10 DR. PINA: I am trying to get a handle on the
11 thrombotic rate in the patients in VIGOR. Dr. Targum, you
12 did an assessment. In your evaluation of the packet that we
13 have you have a table of patients who perhaps should have
14 been on aspirin because they had significant risk factors
15 for thrombotic events and patients that did not. It was a
16 little bit confusing to me. Can you clarify that? What was
17 your understanding of separating the patients that way?

18 DR. TARGUM: I am at somewhat of a disadvantage by
19 not having it in front of me, but what I was presenting was
20 an analysis that the sponsor had done which I, frankly,
21 thought had limitations. I thought it was slicing the data
22 -- I thought we had it so that I had something to refer to.
23 When I looked at the safety update I noticed that the
24 confidence intervals for both the aspirin indicated and
25 aspirin not indicated subgroups still were consistent and

1 that they were against rofecoxib and favored naproxen,
2 regardless of whether aspirin was indicated or aspirin was
3 not indicated. So, my feeling is that, regardless of
4 whether you take that post hoc subgroup or not, the trend
5 was against rofecoxib.

6 DR. PINA: Thank you for the clarification.

7 DR. VILLALBA: This is from my briefing document
8 and this is the data that you are referring to, and it shows
9 that for that subset of patients, retrospectively identified
10 as candidates for secondary prevention, the risk was five
11 times higher for rofecoxib. For those who were not at risk,
12 who were the majority, the risk was still twice.

13 DR. REICIN: Can I show one slide, slide 1449?

14 [Slide]

15 You are correct, the risk was reduced in the
16 naproxen group whether patients had "an indication" for
17 aspirin or not. Early on, before we did the safety update
18 report, most of the risk was in the aspirin indicated group.
19 With the safety update report it was more evenly
20 distributed.

21 [Slide]

22 One thing that struck me in reviewing the data --
23 this is in the APCT endpoint in those for whom aspirin
24 therapy was indicated -- if you go over to the naproxen
25 group you can see that these are patients who had a prior

1 MI, prior angioplasty, CABG, and there were no myocardial
2 infarctions in that group and that was one of the things
3 that was surprising to us.

4 DR. HARRIS: Thank you. Okay?

5 DR. LIM: I am Stan Lim, FDA statistician. I just
6 want to get back to the issue about the inflection point and
7 whether that is real or not. I don't think you can really
8 answer that question based on statistics but I would point
9 out that VIGOR is a rigorously defined, long-term trial and
10 we see what we see. Now, Dr. Li also presented some data.
11 I mean, granted it is not something that we had realized in
12 depth, but we took data from the sponsor and put it in table
13 form to compare rofecoxib 50 mg versus naproxen versus
14 diclofenac and ibuprofen. If you remember that slide, it
15 says that if you look at data that are six months or longer,
16 there appears an increased risk.

17 DR. ZEGER: I just wanted to make the point that I
18 was not saying this proves that there is no change. I was
19 just trying to be responsive to the question. Is there
20 strong evidence in the data of a change, and my answer to
21 that is no.

22 DR. HARRIS: Thank you. Dr. Harrell?

23 DR. HARRELL: On that point, I think if today and
24 yesterday we never saw a single point estimate or a single p
25 value or a single power calculation but only saw confidence

1 intervals we would be so much better off than we are right
2 now. But on this particular graph what we need to see is a
3 confidence band for the hazards ratio over time. It is a
4 real easy graph to make and I hope somebody has made it.

5 DR. HARRIS: Thank you.

6 DR. SAMPSON: Dr. Goldkind, I was wondering -- I
7 know it is dangerous to compare across studies and
8 populations, and maybe you can correct me, the complicated
9 PUBs today I should think of as the POBs of yesterday. Is
10 that correct?

11 [Laughter]

12 DR. GOLDKIND: It is dangerous to cross compare.
13 Again, there would be confidence intervals around each
14 definition. Actually, if sponsors from yesterday or today
15 want to make comment after I do, that would be fine. I
16 think that the PUB today would be, in a rough sense, the
17 complicated -- the POB, I am sorry, the complicated POB
18 would be closer to the complicated ulcer. The PUB which
19 included symptomatic ulcers would be the composite endpoint
20 that was looked at yesterday, although, again, there were
21 some definitions -- how close they would be if you kind of
22 used the definitions from one to the other, I am not sure.

23 DR. SAMPSON: To follow up on this, and again I
24 recognize that yesterday's study was done in a mixed
25 population of RA and OA, but there is something that you

1 folks pointed out yesterday -- and, again, please correct me
2 because I am looking at sketchy notes here -- yesterday you
3 pointed out that the Celebrex PUB rates continued to rise
4 after six months, while diclofenac and ibuprofen seemed to
5 flatten out. Today we see the Vioxx rates rising after six
6 months and the naproxen rates also rising after six months.
7 I was wondering if you would have any comment about why
8 biopharmaceutically the naproxen rates would continue to
9 rise while the diclofenac and ibuprofen remained somewhat
10 flat.

11 DR. GOLDKIND: Actually, the pattern seen
12 yesterday for the composite of symptomatic and complicated,
13 which would be the equivalent of the PUB, again a lot of
14 confidence intervals and all the qualifications of cross
15 comparing, but yesterday that composite actually did show
16 that events continued to accrue in all three groups looking,
17 in general pattern, similar to what was seen here. So, the
18 question would be complicated ulcers appear to manifest
19 themselves earlier in the NSAID comparators in the CLASS
20 study, whereas in this database that wasn't seen, and I
21 don't have any answer for why the complicated ulcers -- you
22 know, there are a lot of possibilities.

23 DR. SAMPSON: You wouldn't want to ascribe it to
24 study basis versus drug basis? Hard to say?

25 DR. GOLDKIND: It is hard to say because there are

1 issues of informative censoring. Yesterday the sponsor
2 alluded to whether that would have played a role. What I
3 think we have learned in these large, simple trials is they
4 may be large but they are not simple and there are so many
5 factors that would play into why you may see change over
6 time -- it is too complicated, I think, for me to venture an
7 intelligent answer.

8 DR. HARRIS: Thank you.

9 [Slide]

10 DR. VILLALBA: This shows the confidence interval
11 for all patients randomized. The estimate is 237 and the 95
12 percent confidence interval is here and that is the p value.

13 DR. HARRELL: What I was talking about was the
14 instantaneous hazard rate at a given time estimated for a
15 lot of different times with confidence interval on it.

16 DR. ZEGER: This is Scott Zeger again. Just in
17 response, what I actually did was exactly what you are
18 saying. I estimated a relative rate within each of two-
19 month intervals and I can give you that after lunch.

20 DR. HARRELL: Just to be nit-picky, Scott, I don't
21 want it in two-month intervals but I want it as continuous,
22 you know, smoother --

23 DR. ZEGER: Right, that would be even better and I
24 can't give that to you after lunch.

25 DR. HARRIS: Thank you. I think we must push on.

1 We are moving now to our open public hearing, and Dr. Sidney
2 Wolfe, Director of Public Citizen Health Research Group, has
3 a statement.

4 Open Public Hearing

5 DR. WOLFE: I just want to talk about three
6 things, one, the GI toxicity or reduction in it; two, the
7 cardiovascular problems; and just an overview on how we got
8 into this mess that we are in right now.

9 There are three ways in which the group in the
10 VIGOR study differs not only from the general population but
11 from a lot of other things. One, it was just rheumatoid
12 arthritis and, given that the drug isn't even approved for
13 that, the typical user of Vioxx can hardly be construed as
14 someone with rheumatoid arthritis.

15 Secondly, the percentage of people -- 56 percent
16 of the people in the study were takings steroids for their
17 rheumatoid arthritis. This is almost twice as high as the
18 percentage taking steroids in the CLASS study.

19 Third, a comparator drug was used which clearly is
20 not one of the two safest drugs. A chart that I distributed
21 yesterday is a review of all the case control studies on all
22 the NSAIDs. In six of the seven comparisons ibuprofen
23 turned out to be safer than naproxen. It was tied in the
24 seventh. In five of the seven comparisons diclofenac turned
25 out to be safer. Those two drugs were, therefore, I think

1 appropriate comparators for the CLASS study. They would
2 have been appropriate comparators for this. So, a more
3 dangerous comparator drug is always going to make a drug,
4 such as Vioxx, look better.

5 If one does a subgroup analysis, which the FDA
6 did, very clearly on the issue of the steroids, people
7 taking steroids who were then given naproxen had a much
8 bigger increase in the amount of ulcers than occurred in the
9 group that were getting Vioxx, such that when you looked t
10 the people who didn't take steroids in the study there was
11 not a statistically significant reduction in GI events in
12 the people taking Vioxx who were not taking steroids
13 compared with Naprosyn.

14 So, there are several things that I think cloud up
15 validity of the results on the GI toxicity, and I would
16 argue that if you had taken Celebrex and put it in this kind
17 of study you would have gotten probably very similar results
18 as far as GI toxicity.

19 As I mentioned yesterday, from what I again
20 described as an exciting paper in the proceedings of the
21 National Academy of Science, and probably a dozen or so
22 other papers in the literature, clearly in the role of
23 healing tissue, including ulcers in this case or any GI
24 tract abnormalities, cyclooxygenase-2 is very important and,
25 therefore, it is not terribly surprising that you really

1 don't do a better job than you would expect from the not
2 representative GI endoscopy studies in getting rid of these
3 ulcers compared to other drugs.

4 As far as the cardiovascular toxicity, someone
5 mentioned some of the other studies in which people were
6 getting aspirin. Yes, there is not a statistically
7 significant increase in MIs but if you combine the two
8 studies, I guess 090 and 085, a total between the two of
9 maybe 800 or so patients in each group for Vioxx and
10 nabumetone, there are four MIs in the group getting Vioxx
11 and only one in the other -- not statistically significant;
12 small numbers and, as was pointed out, short duration but
13 still a suggestion. There are also suggestions from the
14 CLASS study, although again not reaching statistical
15 significance, of an excess of MIs in people getting
16 Celebrex.

17 So, in conclusion of these two points, I would
18 argue that there really isn't any credible evidence of a
19 difference between these two drugs in either their GI
20 toxicity or so-called reduction of serious GI complications,
21 or in their propensity to be associated with a larger number
22 of cardiovascular events, including MIs. I think that the
23 two possibilities, or three, the three being "other" to
24 explain this difference, (a) being the anti-platelet
25 activity that is not present in these drugs and, (b) being

1 prothrombotic activity -- my guess is that when we know much
2 more than we do now both of them will be in place, but I
3 certainly agree that one can hardly explain the results of
4 the five-fold increase in heart attack risk, statistically
5 significant, in the VIGOR study by simply the fact that it
6 lacked the anti-platelet activity of Naprosyn. I mean, what
7 I could see of that case-control study which is a case-
8 control study with all of the flaws inherent in case-control
9 studies compared with a randomized, controlled trial, the
10 risk ratio was 0.6. That is very different from a five-fold
11 increase in heart attacks.

12 Finally, I would like to say that the FDA has done
13 an extraordinarily good job in reviewing and presenting this
14 massive amount of data, such that the next time one of these
15 drugs comes along I think these studies should be required
16 before approval. There is no reason why studies lasting
17 six, eight, nine months on an important safety issue should
18 not be required for drugs that don't arguably have any
19 safety advantage over other drugs. There is absolutely
20 nothing in the evidence prior to approval to suggest that
21 these drugs, from an efficacy standpoint, were a
22 breakthrough and there certainly should have applied long
23 ago to other drugs but we now know more than we did. I
24 think particularly the increased risk of cardiovascular
25 problems behooves the FDA to require safety drugs. We are

1 not talking about ten-year studies; we are talking about
2 studies that are six, eight, ten months, that should be
3 done.

4 I believe that a massive fraud has been
5 perpetrated on people in this country who have spent
6 billions of dollars on drugs that are not arguably any
7 better, to the extent that Celebrex didn't even make the
8 grade in terms of its pain relief. It was not approved
9 initially for that. And, we have not yet seen the data that
10 would justify approving Vioxx for rheumatoid arthritis. To
11 sell a drug based on some interesting, but in the larger
12 picture I don't think that relevant GI problems that are
13 somewhat relieved, is really to mislead people. I think
14 that the emphasis has been in the presentation that I saw
15 this morning on overall safety. The enzyme is present all
16 over the body. It is going to have what turn out to be
17 adverse effects in many other organs and tissues, which I
18 suspect will come in studies in the next couple of years,
19 and I just hope that everyone learns from this and the next
20 time something like this occurs these studies will be done
21 prior to approval instead of afterwards. Thank you. If you
22 have any questions, I would be glad to answer them.

23 DR. HARRIS: Thank you very much, Dr. Wolfe. If
24 there are no other comments from the public, I would like to
25 move towards adjourning this session but before I do so, I

1 am wondering if I can ask everybody, as precise as one can
2 be, that we get back here at 1:15 p.m. We are running a
3 little late and I am going to give you about 55 minutes for
4 lunch. Thank you.

5 [Whereupon, at 12:20 p.m., the proceedings were
6 recessed, to be reconvened at 1:15 p.m., this same
7 day.]

1 A F T E R N O O N P R O C E E D I N G S

2 DR. HARRIS: I would like to call the afternoon
3 session to order.

4 **Discussion and Questions**

5 **Vioxx Questions**

6 This afternoon we are going to consider the
7 questions that have been posed to us by the FDA. I am going
8 to start immediately with question one.

9 Please comment on the differences in
10 cardiovascular event rates between the Vioxx 50 mg and
11 naproxen groups. Are further studies warranted? Does this
12 finding warrant consumer/prescribe awareness? If so, in
13 what format?

14 So, there are several questions. I agreed, as we
15 did yesterday, to start with our experts and we are going to
16 start with our cardiovascular experts, and Dr. Steven Nissen
17 would like to present some data.

18 DR. NISSEN: Thank you. First of all, I
19 appreciate the opportunity to be here. Obviously, this is
20 an issue that crosses several different disciplines and, as
21 one of the two cardiologists here, I thought it would be
22 appropriate if I helped the committee to think through what
23 we have seen here in the cardiovascular data and maybe talk
24 a little bit about what I think the implications are.

25 [Slide]

1 I think we are all aware of what the data shows
2 but I want to reiterate it, particularly for three what I
3 would call hard endpoints, cardiovascular death, myocardial
4 infarction, stroke and the composite of those three. I took
5 these data from the report. I don't have access to the
6 database and I want to say right from the very beginning
7 that I have neither shared this data with the agency or
8 anyone else here. This is my own analysis of the data.
9 Take it as you will and, obviously, I may not have exactly
10 the numbers correctly but I certainly did my best.

11 So, the question then that comes up that I think
12 has been in the back of all of our minds is whether or not
13 what we are seeing here in these differences in events is a
14 very low rate in the naproxen group or a very high rate of
15 events in the rofecoxib group. It is a different question
16 to answer, but I think there are some things that can be
17 done that will help answer it.

18 I want to also point out just a couple of things
19 here. At least in my analysis, the acute myocardial
20 infarctions events are really driving a good deal of this.
21 So, that is obviously an important aspect of this.

22 Well, how could we go about analyzing which of the
23 two hypotheses makes more sense? Well, one way is to ask
24 the question whether the naproxen event rates are similar to
25 event rates in patients who receive aspirin with similar

1 demographics, and also ask the question whether the
2 rofecoxib event rates are similar to the event rates of
3 patients who don't take aspirin, who are on placebo, in a
4 similar risk category.

5 Let me say from the outset that I am well aware,
6 as all of you are, of the limitations of this sort of
7 statistical analysis, and I will not even suggest that it
8 means more than, if you will, a reality check that may help
9 us to understand the data a little bit better. This is not
10 hard science and it is not necessarily, you know, good
11 statistics.

12 [Slide]

13 In looking at this to try to, at least in my own
14 mind, get to some comfort level, I was able to identify a
15 study, recently published, that has demographics that are in
16 the same ball park, and this is the primary prevention
17 trial, or PPP -- Primary Prevention Project, published in
18 Lancet really only a few weeks ago, which was an aspirin
19 versus no aspirin trial in about 4500 low risk Italian
20 individuals who had at least one cardiovascular risk factor.
21 However, included in those risk factors was age greater than
22 65. So, if you were over 65 you were deemed to have a
23 cardiovascular risk factor. They had no prior MI or stroke.
24 The mean age was 64 years. There were more females than
25 males, which again had some similarities to the database in

1 the VIGOR trial. Fifteen percent were current smokers,
2 which is amazing because anybody who has been to Italy --

3 [Laughter]

4 -- I can't imagine anybody could find an Italian
5 population that only had a 15 percent tobacco use, and 68
6 percent had hypertension.

7 [Slide]

8 Is this a reasonable comparison? Well, as you
9 would expect, there are differences. Compared to VIGOR this
10 population is six years older. That is reflected here.
11 More of them were over the age of 65. The female
12 predominance is a little bit less. They had more
13 hypertension. The VIGOR patients were a little bit more
14 likely to be smokers, and the PPP patients were a little bit
15 more likely to be diabetic.

16 Again, these are all limitations of comparing two
17 different trials and, again, I really want to be cautionary
18 about any analysis of this kind, but I think we have to do
19 this if we are going to have any idea of whether any of this
20 makes any sense or not.

21 [Slide]

22 In the PPP trial there were statistically
23 significant reductionism in events. That is, cardiovascular
24 death, MI, stroke and the composite of the two. You can
25 read the Lancet paper. I won't give you the confidence

1 intervals and so on. I actually have a copy for anybody
2 that would like to look at it.

3 Is it legitimate to compare the aspirin arm in the
4 PPP trial to naproxen and the placebo arm to rofecoxib? I
5 will let you be the judge of that. I am, however, aware of
6 several things, that the comparison of two trials in
7 different populations is inherently risk. The definitions
8 of risk factors such as hypertension and diabetes are not
9 necessarily uniform between these trials, and even the
10 definitions of cardiovascular endpoints are not necessarily
11 uniform. So, I would consider this analysis exploratory
12 and, at very best, hypothesis generating but not more than
13 that.

14 [Slide]

15 What did we see here? Well, it is a bit
16 reassuring that the naproxen event rates in VIGOR and the
17 aspirin event rates in PPP were very, very similar. If you
18 do the confidence intervals here, these are really amazingly
19 close. Cardiovascular death, MI, stroke and the composite
20 in the VIGOR trial with naproxen and the aspirin arm of PPP
21 were very similar. This, to me, provides some reassurance
22 that what we may be seeing here, at least in part, is a
23 protective effect of naproxen. If the event rates in the
24 naproxen arm had been significantly different from the
25 aspirin arm in PPP, I think the whole analysis would be much

1 more different.

2 [Slide]

3 What about the rofecoxib versus no aspirin? Well,
4 the cardiovascular death rate in the PPP trial was a little
5 bit higher. The MI rate in the rofecoxib group compared to
6 the no aspirin or placebo arm of PPP was higher. So was the
7 stroke rate and so was the composite endpoint rate.

8 I think it is important to point out, what was not
9 discussed here and I think should be discussed here, that I
10 also looked at the MI rate in the CLASS trial with celecoxib
11 and noted that these rates were quite similar in rofecoxib
12 and in the CLASS trial. I think that is perhaps an
13 important point for discussion.

14 [Slide]

15 What about the confidence intervals around these
16 comparisons? If you assume that rofecoxib and no aspirin in
17 PPP are the same, and look at the differences and then look
18 at the 95 percent confidence intervals around the
19 differences, this is what you see -- p value for death, not
20 significant; p value for MI appears significant, and I use
21 the word significant in quotes because these are two
22 different trials. CVA, no difference, and a trend in the
23 composite data towards significance.

24 [Slide]

25 If I graph these, with no difference being this

1 line, here, you will see that the confidence intervals for
2 death cross this line. There is an excess of myocardial
3 infarctions comparing rofecoxib to no aspirin. But stroke
4 and the composite endpoint don't get to statistical
5 significance.

6 So, again, within the limits of this type of
7 analysis, there wasn't, in my view, except in the area of
8 myocardial infarction, a very strong signal.

9 [Slide]

10 What can we say then in conclusion? Well, the
11 cardiovascular event rates for naproxen in VIGOR and for
12 aspirin in PPP in relatively similar populations were low,
13 and they were virtually identical. This would tend to
14 support the hypothesis of a protective effect for naproxen.
15 The event rates for rofecoxib are higher than the no aspirin
16 arm of PPP, but there were pretty broad confidence intervals
17 here, particularly when you consider that we are looking at
18 two different populations.

19 Only the differences in MI rates are significant,
20 but there were very few events. I would point out to
21 everyone at the table that in the entire cohort there were
22 only 24 myocardial infarctions, 20 in the rofecoxib group
23 and four in the naproxen group. A shift of two or three MIs
24 could easily have made a difference here in terms of the
25 outcome with respect to this analysis. So, we are really

1 talking about a very, very few events.

2 Accordingly, the possibility of higher event rates
3 comparing rofecoxib to placebo can't be excluded but I
4 think, on the basis of my analysis here, this certainly does
5 not prove it. I think it is also important to note that
6 there are essentially identical MI rates for celecoxib and
7 for rofecoxib in VIGOR.

8 [Slide]

9 What do I think we ought to consider doing here?
10 Well, I think the absence of a cardioprotective effect for
11 both COX-2 inhibitors should be emphasized in the product
12 literature. There is nothing I have heard either yesterday
13 or today which suggests that either agent has a
14 cardioprotective effect as do the non-selective agents, and
15 I think that must be emphasized in the product literature.

16 I think we need further studies to investigate
17 whether there is an excess of cardiovascular events in
18 longer term exposure to both of these agents in comparison
19 to placebo, and I think we need to know whether co-
20 administration of aspirin can reestablish the
21 cardioprotective effects of COX-1 inhibition without
22 increasing the GI morbidity. I think those two questions
23 have simply not been answered by any of the data that I have
24 seen and I personally think we need a 2 X 2 kind of a
25 factorial design study to be done where patients receive a

1 COX-2 inhibitor with or without aspirin and we try to find
2 out what happens to event rates on both the GI side and the
3 cardiovascular side when we do so.

4 I do think that these data suggest to me that at
5 least some of the difference between rofecoxib and naproxen
6 is due to naproxen benefit. I mean, that would be one
7 conclusion that I feel reasonably comfortable with. Whether
8 all of it can be attributed to that, I think you will have
9 to make your own mind up about. Thank you.

10 DR. HARRIS: Thank you very much, Dr. Nissen. Can
11 I make one comment again? I mean, this is merely data that
12 is presented. It is very limited. There are obviously a
13 number of reservations which you have mentioned. I want to
14 reemphasize that. So, in terms of our deliberations, I
15 really don't want it to rise to the level of other data that
16 we have seen today.

17 DR. WILLIAMS: However, I think that what you
18 summarized really summarizes my thinking with regard to what
19 we have seen here, with one caveat, and I think that your
20 first recommendation gives the implication that there is
21 cardioprotective effect from the other NSAIDs and I don't
22 think we have evidence for that effect, except what we have
23 seen here on naproxen.

24 DR. NISSEN: Let me say I meant aspirin rather
25 than other NSAIDs.

1 DR. HARRIS: Dr. Pina?

2 DR. PINA: I think Steve has also summarized my
3 feelings about this, and my further concern and confusion
4 relates again to this population which would have been a
5 lower risk population to begin with. And, in this lower
6 risk population -- even though when they went back and the
7 FDA went back, there were patients who probably should have
8 been on aspirin, that had some indications for being on
9 aspirin, the population that will be using this will
10 probably be the population with all the cardiovascular
11 events. This is very similar to what we saw yesterday. In
12 spite of that population being lower risk, I think that the
13 rate of embolic events is still higher than what I would
14 expect in this population.

15 I agree that probably naproxen is giving some
16 anti-platelet effect and that accounts for some of the
17 difference, but I don't think it accounts for the entire
18 difference.

19 DR. HARRIS: Does anybody else on the committee
20 want to comment on the differences?

21 DR. SAMPSON: Dr. Nissen, could you just comment
22 for the non-physician on the difference in effect of a
23 population having RA and the Italian population in terms of
24 the events that you described?

25 DR. NISSEN: We just don't know, Allan. You know,

1 I think that when you compare two different populations this
2 is statistically very hazardous. That is why I was very
3 careful to say that this is just exploratory. I think that
4 we don't know what the native events rates are going to be
5 in these populations. So, there is a lot that we just can't
6 extrapolate from any analysis of this kind, and I really do
7 want to emphasize what Nigel said as well, that, you know, I
8 needed to do this just for my own kind of reality testing
9 here because I needed to know were these event rates that we
10 are seeing with rofecoxib -- were they way out of line with
11 what we might expect in a population like this? I guess
12 what I saw was they really weren't way out of line. They
13 were maybe statistically greater but I think it is jut not
14 proven yet to my satisfaction.

15 DR. HARRIS: Can I say something because there is
16 a comment from the sponsor? I have to say that you
17 mentioned two drugs here, and I am really torn right now
18 because I think the representatives from Celebrex are not
19 here -- but they are here but not in the line. So, I made a
20 decision to allow you to make this statement. I think so
21 far as the committee goes, I will accept comments but my own
22 view is that I don't want to push it any further. That is
23 why I say I don't want it raised to the level of the data
24 that we have seen this morning. Nobody has had a chance to
25 really examine this, and so I really don't want it to be

1 overemphasized. Now, if there is a view about that on the
2 committee, of course, I am prepared to hear otherwise.

3 DR. WILLIAMS: My comments were not based on his
4 data. I thought what he presented summarized the way I feel
5 about the other data that I have heard, that I think there
6 has been good evidence that naproxen may have an effect on
7 cardioprotection, and I think that we have not yet
8 demonstrated that rofecoxib has a negative effect but there
9 seems to be a trend in that direction and more study is
10 needed.

11 DR. HARRIS: Oh, I have no problem with your
12 comment. I think my problem is, you know, in terms of
13 getting any other comment from sponsors or the FDA because
14 we have not had a chance to look at this data and really it
15 is just informal discussion here.

16 DR. PINA: I just want to go back to Dr. Sampson's
17 question about rheumatoid arthritis. There is a certain
18 number of patients, let's say, with long-standing rheumatoid
19 arthritis who can have coronary arteritis and, therefore,
20 can have myocardial infarction events based on the
21 arteritis, but it is not the common presentation and it is
22 usually long-standing disease in a much older population,
23 pretty much severe disease. In most of the rheumatoid
24 arthritis that we see in practice we don't see a lot of
25 coronary events or they come to us with coronary events and

1 we find out they have rheumatoid arthritis. I just wanted
2 to follow up on the pathology.

3 DR. WILLIAMS: Just a comment, there is an
4 increased risk of cardiovascular events in rheumatoid
5 arthritis patients irrespective of vasculitis. Part of that
6 is induced by the use of corticosteroids; part of it is
7 induced by the chronic inflammatory state, and so forth.
8 So, I would not say that it is only coronary vasculitis that
9 would add the risk. There is a basic increased risk in
10 cardiovascular events in rheumatoid arthritis.

11 DR. GUESS: Excuse me, I am Harry Guess, from
12 Merck, and this is a perfect time -- we have looked at the
13 literature on this and, actually, using the general practice
14 research database we examined the risk of thromboembolic
15 events in OA and in RA, adjusting for age and sex, and
16 adjusting for other factors, and we have confirmed what Dr.
17 Williams said exactly. It is about a 1.5-fold increase in
18 RA versus OA. So, I feel, in our hands looking at it, it is
19 consistent with what has been seen in the literature and
20 there is an elevated risk in the RA population. Thank you.

21 DR. HARRIS: What I am going to do -- you have a
22 comment? Sorry.

23 DR. CALLAHAN: I was just going to agree with
24 Jim's comments. There is an increased risk.

25 DR. HARRIS: I want to pose the first question to

1 the voting members of the committee, which is, are further
2 studies warranted? Based on the data we have seen today,
3 would you recommend that there be further studies? Are they
4 warranted? Dr. Wolfe, maybe we could start with you.

5 DR. WOLFE: Actually, at this point, as was
6 mentioned yesterday, we have to bring both of these
7 together. We have to because there are two different
8 studies which look at the impact and actually bring out the
9 importance potentially of aspirin causing a lot of these
10 problems. We can't say with certainty because of the
11 statistical analysis. But, I would like to see some
12 information with these studies on what happens if we do add
13 aspirin to the mix for the people who were actually in need
14 of taking aspirin -- to make this a real-life study. People
15 who are elderly do need aspirin very commonly for cardiac
16 prophylaxis. I would like to see what happens to the
17 protective effects in the GI tract with aspirin.

18 Additionally, I think the FDA has to address the
19 issue of the NSAID comparators. This has been brought up.
20 You know, is there an advantage because we are looking at
21 naproxen in this study comparing rofecoxib because naproxen
22 has the higher toxicity? Or, was there a disadvantage at
23 looking at ibuprofen? If there is some standardization we
24 can compare apples with apples or Macintosh apples with
25 certain types of oranges rather than different types of

1 apples and different types of oranges. So, I think there
2 has to be standardization before we can really compare
3 these. The reality is whether we compare them or not,
4 people in the community will compare these.

5 DR. HARRIS: Dr. Pina?

6 DR. PINA: I think we need more information and
7 even this last point about rheumatoid arthritis -- I think
8 that the rheumatologists probably see the patients with the
9 more severe disease. They get referred to you and on our
10 end, on the cardiac end we just don't see that many patients
11 like that. So, it may be the patient population as I think
12 is the case in this trial. It is a very different
13 population. I think the database is rich and I think we
14 have learned a lot from this database, very well presented,
15 but it just elevates a whole series of questions again.
16 What will be the use of this drug in the general population
17 that will tend to have a lot of cardiovascular co-
18 morbidities and will need aspirin?

19 So, would definitely say that, yes, further
20 studies are warranted. Again, I compliment the sponsor on
21 the richness of the data that they presented to us today.

22 DR. HARRIS: Dr. Nissen?

23 DR. NISSEN: I think, as I said earlier, I really
24 do think it warrants further study, and I think that the two
25 issues for me are do the COX-2 inhibitors -- does rofecoxib

1 increase cardiovascular events over placebo? That is a
2 question that I think we have to know. Secondly, can we
3 neutralize that effect by giving a low dose aspirin, but at
4 what cost in GI toxicity?

5 Those two questions, I do think, are still open
6 questions that the data doesn't allow us to answer
7 currently, and I think for the clinicians who treat both
8 heart disease patients and patients at risk of heart
9 disease, and people who treat patients that have arthritic
10 disorders, those questions simply have to be answered.

11 MS. MCBRAIR: I keep looking at this from the
12 viewpoint of the patient and what kind of knowledge
13 theoretical patient is going to have when they walk in the
14 doctor's office as to what they would like to have happen
15 for themselves, as well as what the physicians are going to
16 need to know in order to make the best decisions possible to
17 prescribe the medications that may help the patient live
18 with arthritis, as well as not have too many adverse effects
19 along the way.

20 I guess I really do feel that there needs to be
21 more study in this area, and I am struck both days with the
22 lack of standardization of the two studies, the lack of
23 standardization of what side effects are, what untoward
24 effects are when we are trying to make these judgments, and
25 the lack of standardization of how we compare these two

1 drugs, how we would look at the whole picture. So, I just
2 would encourage a lot more study here and us really taking
3 time to think through what has been done and how to best
4 proceed from here.

5 DR. WOFSY: I certainly agree that further studies
6 are warranted specifically in this area, but I also want to
7 make the point that further studies are always warranted.
8 It is hard to imagine any presentation to this committee
9 that wouldn't raise important questions. So, I think in
10 focusing on the need for further studies it is also
11 important to keep in mind that we have now seen in this
12 meeting over the two days two large, well constructed,
13 carefully done studies that address the important questions,
14 and there is important information in these studies as well
15 as unanswered questions. I recognize that that would be an
16 important part of what we do this afternoon and I just want
17 to reemphasize by saying that, of course, further study is
18 indicated but my own view is that there is information here
19 that is important to share with the public and with people
20 who prescribe these medications, and there are important
21 things learned from these studies, as well as questions
22 raised.

23 DR. CALLAHAN: I agree with what has been said
24 today. I do think there is a need for further studies, but
25 I would like to reiterate the point that was just made,

1 there are useful data in both of these studies and we need
2 to share that information with prescribers and consumers,
3 and keep Wendy's point in mind, that the bottom line is what
4 is best for the person with arthritis.

5 DR. HARRIS: In my particular case, I certainly
6 feel that there should be further studies. I have to think
7 that as a rheumatologist, as any physician really, since one
8 isn't sure -- and I can't say hearing anything today makes
9 me absolutely sure whether or not we are seeing a protective
10 effect from naproxen or whether or not there is some sort of
11 excess cardiovascular mortality here -- what does one do if
12 you are confronted with a patient with rheumatoid arthritis,
13 which is a population at increased risk, or with some other
14 cardiovascular one, two, three events and you are being
15 asked to prescribe this drug? What is your comfort level
16 doing this? Do we need to add low dose aspirin? Then, if
17 we do add low dose aspirin, will we cancel the effects of
18 the COX-2 on the GI tract?

19 I would say that there are enough queries raised
20 with some of the data that we have seen today, enough
21 unanswered questions with respect to cardiovascular events
22 here, that I really do think that some form of further
23 studies should be done.

24 DR. WILLIAMS: I have to agree with Dr. Wofsy,
25 there is always a need for more studies but this question

1 has specifically to do with cardiovascular events and I
2 would think that there were two particularly interesting
3 things that I think need further investigation. I have
4 never considered the non-steroidal anti-inflammatory drugs
5 as cardioprotective, and we heard data that suggested that
6 at least one of them may be cardioprotective and we have
7 only got any data at all on three of them, and there are 18
8 or 20 that are out there. So, I do think we need to know
9 what level of cardioprotection is available from the various
10 NSAIDs.

11 The other one is whether or not there is an effect
12 of the COX-2 inhibitors that promotes thrombosis. While
13 there has been a suggestion, I don't think we have the
14 answer to that yet at all either. So, I think that is
15 another area where further studies are necessary.

16 DR. SAMPSON: In terms of new studies, I would
17 concur that further studies are needed. I would concur with
18 Dr. Nissen that there should be placebo controls in those.
19 Low dose aspirin should be a factor in the studies. There
20 should be well chosen NSAID comparators that are meaningful
21 in a broad way. The populations -- I would imagine you
22 would want more than an RA population; you would want a
23 broader population. And, care and thought should be put
24 into the endpoint that one wants to look at and the study
25 duration.

1 In addition, I would go back to what Dr. Wofsy
2 said, and that is that there is a lot of information in the
3 CLASS and VIGOR studies and that there is a wealth of
4 opportunity for people that would like to do some sort of
5 meta-analytical work combining those two studies to try to
6 tease out a stronger effect, or to tease a stronger
7 inference. I don't think we should discard the fact that we
8 have a lot of rich data before us that might provide answers
9 -- some answers, partial answers under further analysis.

10 DR. ELASHOFF: Yes, I do believe there is reason
11 to be concerned about cardiovascular event risks for the
12 COX-2 inhibitors, and I think the one thing I want to add to
13 what has already been said is that further studies need to
14 be done in a timely manner. We don't want to spend a lot of
15 time waiting around until we have a better idea of what is
16 going on here.

17 DR. HARRELL: I will just echo what the last two
18 statisticians said. I think the FDA could also provide
19 maybe a little more guidance in terms of the number of
20 comparators needed in the study and which comparators,
21 duration of follow-up and when, in the course of drug
22 development, the long-term safety studies are needed to be
23 done.

24 DR. HARRIS: An equally different question, in my
25 mind, is does this finding warrant consumer/prescriber

1 awareness? Again, it takes time but I would like to sort of
2 seek opinions of each individual here.

3 DR. WOLFE: This time I want to actually address
4 some of the comments that were made this morning regarding
5 gastrointestinal hemorrhage. This is an impromptu little
6 presentation --

7 DR. HARRIS: Can we hold that for question two
8 because I presume question one is talking about
9 cardiovascular events?

10 DR. WOLFE: That is fine.

11 DR. HARRIS: We are still on question one, the
12 second part of question one is, does this finding warrant
13 consumer/prescriber awareness? This is with respect to
14 cardiovascular events.

15 DR. WOLFE: Yes, I think at this point, from what
16 we have seen, there is enough information that is available,
17 going just on the merit of the study itself -- we have to
18 see what the study showed. The study showed that there was
19 a potential increased risk in thrombotic events,
20 particularly for those who are predisposed.

21 But the biggest message I have, and I mentioned
22 this yesterday, is that the consumer must be warned very,
23 very carefully by physicians that these drugs are not
24 replacements for aspirin for cardiac prophylaxis.

25 DR. PINA: Agreed on both fronts.

1 DR. NISSEN: I think that the question for me is
2 whether there is any evidence here of an excess event rate
3 over placebo, and it is just not on the table. We just
4 don't have any want to answer that. So, what can we say?
5 What we can say is that in this population getting naproxen
6 was associated with a lower cardiovascular event rate than
7 getting rofecoxib. Therefore, it seems to me that what we
8 probably need to do, since we don't really know, is to make
9 it very clear that there is not a cardioprotective effect
10 for the COX-2 inhibitors, and that the decision on whether
11 or not to co-administer aspirin is a matter of clinical
12 judgment. I don't think that any guidance beyond that is
13 possible based upon the data. We don't have the data we
14 need to actually make a final determination of with what we
15 saw was cardioprotective effect of naproxen or excess risk
16 for rofecoxib, and I just think we can't go beyond what the
17 data actually tells us.

18 MS. REEDY: Is that a yes or no?

19 DR. NISSEN: I do think we should modify the
20 current statement but I would be very cautious about how we
21 modify it so that we do not overstate the issue of risk.

22 If I could just amplify on that for a moment, we
23 saw a very strong message about some reduced incidence of GI
24 effects and I happen to share Dr. Wolfe's perspective that
25 these are not trivial events. As I said yesterday during

1 the discussion, to a patient it doesn't matter whether you
2 end up in an intensive care unit with a big GI bleed or
3 whether you end up in an intensive care unit with a
4 myocardial infarction. They are both pretty bad things to
5 have happen. So, I don't want to throw the baby out with
6 the bath water here. What I want to do is say what do we
7 know? We know that there is not a cardioprotective effect
8 for COX-2 inhibitors and we should emphasize that in any
9 revisions that are made to labeling, but beyond that I am
10 not willing to make any statements yet.

11 MS. MCBRAIR: I do think there needs to be some
12 additional information for consumers on the issue of the
13 cardiovascular problems. I would like to see additional
14 studies done. I agree with Janet, and I would very much
15 like that to then help us better guide patients and their
16 doctors.

17 DR. WOFSY: I have two comments, and I fear they
18 may sound contradictory. I am going to try very hard to
19 make it clear that they are not in my mind.

20 The first is a direct answer to your question.
21 Yes, I think that the labeling should reflect these
22 concerns. The second, however, is that I think we are
23 making the mistake in the way we are approaching this , that
24 we would be concerned if somebody came forward to us with
25 this question. We are starting out by focusing on a

1 question that was not the primary endpoint of the study. It
2 has been picked out among hundreds, maybe thousands of
3 things that might have fallen out unexpectedly from this
4 study. So, we find ourselves going around the table talking
5 about whether the label should talk about the
6 cardioprotective effects of non-steroidal anti-inflammatory
7 drugs, and that was not the goal of any of the studies that
8 we have seen.

9 So, having already said that I share the view that
10 one of the things that has come out of this study is a
11 reminder that that is probably an important thing to alert
12 people to, I don't think this should be our starting point
13 for discussion. To just follow through with what the
14 statisticians have emphasized in this meeting, from a purely
15 statistical and methodological point of view, this was not
16 the focus of the study and it is hazardous to make it the
17 central focus of the beginning of our discussion. Frankly,
18 I think we need to be starting with what the prespecified
19 primary endpoints were, and then move to what other things
20 have come out of this that have raised questions in our mind
21 that this study was never designed to answer in the first
22 place.

23 DR. CALLAHAN: I do think the data warrant
24 providing information to consumers and provides. I feel
25 like if the information is out there with all the caveats

1 that it isn't definitive but at least to let people know
2 what is known today.

3 DR. HARRIS: For myself, I too believe that there
4 should be some things in terms of consumer awareness. I
5 toyed between lack of a cardioprotective effect and actually
6 stating what the results were. But, then we only have that
7 with respect to one of the two COX-2 inhibitors. What does
8 one do about another? So, I would waive with respect to the
9 cardioprotective effect.

10 But, following Dr. Wofsy's remarks, here is the
11 issue with respect to these safety studies, period, because
12 you apparently start off with -- I think in this case quite
13 justified because GI toxicity is so important with respect
14 to non-steroidals that you could say, yes, let us start off
15 with a safety study with respect to GI toxicity. But the
16 question is to what degree do other organ systems impact
17 these studies, and to what degree should we be monitoring
18 other organ systems? I think this is really muddy waters
19 and I really think maybe at a separate point the FDA really
20 does need to think through some of these issues with respect
21 to safety trials in the future.

22 DR. WILLIAMS: Interestingly, I agree with
23 everyone but I consider myself a "no." I agree, I don't
24 think we have enough data to make any awareness to anyone
25 yet, other than to say they are not cardioprotective which

1 has never been proposed, at least in my mind, until I got
2 this information. So, I do not think there is anything that
3 we can say yet to consumers or prescribers that has any
4 foundation.

5 DR. SAMPSON: I guess I would stay with Dr.
6 Nissen's point of view, as I heard it, in that there would
7 be a statement about the lack of cardioprotectiveness of
8 COX-2's, plural. Did you use the word "unknown effects" or
9 aspirin, or left it to the physician's judgment?

10 DR. NISSEN: Yes, something to that effect. I
11 mean, I think the word crafting obviously is a subject to a
12 lot of discussion.

13 DR. SAMPSON: But the notion that even aspirin is
14 questionable to counter the lack of cardioprotectiveness.

15 DR. NISSEN: Right, we don't know what the risk or
16 benefit of adding aspirin is.

17 DR. ELASHOFF: I think I would feel that something
18 stronger than just saying there is a lack of
19 cardioprotective events is warranted, although it is true
20 that there are many other possible safety things that could
21 have been looked at, and there is no p value protection, the
22 p value was not just sort of 0.047; it is quite marked.
23 There is consistency across several different similar
24 diagnoses within this study. There is consistency with some
25 of the Phase III data. There is consistency with

1 yesterday's data. So, I think while one doesn't want to
2 claim that something has been proven at this point, there is
3 more than just one piece of evidence and they all kind of
4 tie together.

5 DR. HARRELL: I agree strongly with what Dr.
6 Elashoff just said, and I think that the price of having
7 only one comparator in the study is that we only have the
8 good safety data against that comparator but there needs to
9 be very specific and strong safety warning in the labeling
10 with regard to cardiovascular risk against naproxen. I
11 would go a step further to say that the FDA should consider
12 a labeling restriction with regard to cardiovascular risk
13 factors. Until the other study is done, if it is ever done,
14 the best data that we have now is that patients that have
15 cardiovascular risk factors, of which age is a strong one,
16 may be at risk, extra risk. And, I think there needs to be
17 an assessment somehow according to age and number of risk
18 factors beyond which the patient is an unsuitable candidate
19 for the drug.

20 DR. CRYER: Dr. Harris, if I might chime in on
21 this at this point --

22 DR. HARRIS: Go ahead.

23 DR. CRYER: Thank you. I have sat and kind of
24 listened to the discussion that has gone around and even
25 though I am not a cardiologist, from a consumer and

1 prescriber perspective, all I have heard is that really
2 there seems to be most definitively not a cardioprotective
3 effect that is provided by the COX's and that the strongest
4 recommendation that I think one can make on the basis of the
5 data, at least that I have seen, is that in people who
6 required cardiovascular protection with low doses of aspirin
7 should be given low doses of aspirin.

8 I heard placed out for discussion that maybe it
9 should be stated what the results actually were with respect
10 to cardiovascular issues, and at least the concern that I
11 have with respect to that is that we, as a group of experts
12 or you as a group of experts with respect to this issue,
13 haven't been able to decide what the data say. So, that
14 would make it even more confusing for a prescribing
15 physician or even more so for a consumer to actually reach a
16 conclusion with respect to the data if you were actually
17 going to include it.

18 Finally, from a gastroenterologic safety
19 perspective, again I want to just ditto the comments of Dr.
20 Wofsy in that the whole emphasis for the development of
21 these compounds was really because we had a safety need with
22 respect to gastrointestinal events with traditional NSAIDs,
23 and with regard to cardiovascular potential warnings I don't
24 want us or the prescribing physician to potentially lose
25 sight with respect to the data that we have seen today what,

1 in my opinion, is a clear gastrointestinal benefit.

2 DR. HARRIS: Actually, this question has a third
3 part but my sense -- and I am going to turn to the FDA -- is
4 that we have gotten consensus and enough information that
5 would guide the format. Unless there are any burning views
6 otherwise, I want to go to number two.

7 I am going to proceed to question number two.
8 Given the potential effects of concomitant aspirin use on GI
9 and cardiovascular outcomes and the large population of
10 patients for whom both anti-platelet and analgesic; anti-
11 inflammatory agents are indicated, what guidance should be
12 given at this time regarding the concomitant use of aspirin
13 and Vioxx? There is a second part, are additional studies
14 warranted? I guess, Dr. Wolfe, maybe we could start with
15 you.

16 DR. WOLFE: Thank you.

17 [Slide]

18 As I said to the group, many of us here in
19 gastroenterology feel like Rodney Dangerfield in that enough
20 emphasis is not being placed on upper GI hemorrhage. I
21 actually agree. I think that we should have started with
22 the primary objective of the study, but the prerogative of
23 the chair was to start with the other topic first.

24 But, again, this is not a trivial issue. If you
25 look at mortality for upper GI hemorrhage, it is 8-10

1 percent and it is unchanged since early 1930's. Now, that
2 implies that we are not doing any better with all the fancy
3 equipment we have. I should also stress that we have some
4 real experts here on GI hemorrhage who have done many
5 studies and are true experts in this area so I will be
6 quoting some of the work that they have done.

7 But one of the reasons that it hasn't changed is
8 that we are seeing sicker people survive longer, and also we
9 are seeing people just live longer and mortality and age are
10 related logarithmically.

11 [Slide]

12 I just concocted this real quickly, just using a
13 10-year old with a bleed which is a little young, but
14 actually I have seen 20-year old NSAID bleeds. If you look,
15 you start with 1X. You go quickly to 2, to 4, obviously to
16 8. You really increased quite significantly and we are
17 seeing people who are much older have these problems.

18 [Slide]

19 The other thing, after talking to some of the
20 cardiologists here, is that mortality from GI hemorrhage is
21 similar to those patients who are actually hospitalized with
22 acute myocardial infarction. Now, MI is a very sexy disease
23 where, you know, GI bleeding is dirty.

24 [Laughter]

25 But I tell you it is very, very serious.

1 Additionally, and I mentioned this yesterday, 13 percent of
2 upper GI bleeds are associated with MI. Steve mentioned
3 before that a patient is hospitalized either with a GI bleed
4 or MI but they could be with both. Believe me, we all see
5 it all the time. This is not trivial. Some people who die
6 at home with an MI or CVA maybe had a GI bleed precipitating
7 the problem in the first place.

8 Risk factors for mortality include age and
9 concomitant serious illness, as I mentioned, similar to the
10 proportion of the population of patients receiving NSAIDs.

11 [Slide]

12 These are the risk factors, but what always comes
13 out are previous ulcers and age.

14 [Slide]

15 This is one of many, many studies showing this and
16 it is logarithmic. We start seeing increase in mortality by
17 age from the late 20's and it reaches statistical
18 significance in the early 50's. But, you can see in this
19 group between 70 and 80 the relative risk is 5.6. That is
20 the population with a lot of NSAID use.

21 [Slide]

22 I am almost done. Most common GI emergency by far
23 is upper GI hemorrhage. At least 50 percent of GI bleeds
24 are due to ulcers, and we see the vast majority of ulcer
25 bleeds associated with NSAID use, in this 80 percent range.

1 Thus, just three reasons explain excess mortality
2 due to NSAID-induced hemorrhage. First of all, the elderly
3 use NSAIDs more commonly. Age is a risk factor for NSAID-
4 related ulcer bleed. Mortality due to hemorrhage increases
5 with age. So, it is a significant problem which is the
6 reason the study was done in the first place. We can't lose
7 sight of that. Thank you.

8 DR. HARRIS: Thank you so very much, Dr. Wolfe. I
9 am going to ask you the question again --

10 [Laughter]

11 -- what guidance should be given at this time
12 regarding the concomitant use of aspirin and Vioxx?

13 DR. WOLFE: I looked at this question very
14 carefully and that is one reason I gave this. There are no
15 data in the study to look at this. So, everything is
16 conjecture; it is hypothesis. That is one of the reasons I
17 think the second part of this question, are additional
18 studies warranted -- absolutely. We have to see what
19 happens. Do we lose the protective effect to the GI tract
20 by adding aspirin? Actually, my last slide was, indeed,
21 showing that aspirin at low doses, as we mentioned
22 yesterday, carries a risk of 2.3. There is no reason to
23 suspect that using a drug which potentially could increase
24 thrombogenic effects would counteract this. The effect will
25 be on the platelet itself to decrease thromboxane and the

1 bleed will then probably occur. So, this is all conjecture,
2 all hypothesis. I don't think we can say anything about the
3 concomitant use but I would like to see that study done.

4 DR. HARRIS: Dr. Cryer?

5 DR. CRYER: I agree with Dr. Wolfe's comments, but
6 with respect to your specific question about additional
7 guidance, I just reviewed the current label with respect to
8 the current guidance that has been given and what you say
9 under aspirin is concomitant administration of low dose
10 aspirin st Vioxx may result in an increased rate of TI
11 ulceration or other complications. Based upon the data that
12 exist, I think that is all we can currently say, and I think
13 it has already been sufficiently said.

14 DR. HARRIS: Thank you very much, Dr. Cryer. I am
15 going to go around the room and ask for brief comments with
16 respect to concomitant use of aspirin and Vioxx with respect
17 to guidance.

18 DR. PINA: I think that clinical judgment is going
19 to have to be the rule for the individual clinician with an
20 individual patient. Putting in a sort of balance the risk
21 of bleeding, the need for concomitant aspirin, how salient
22 are the cardiovascular risk factors, and how bad the need
23 for the discomfort and the pain associated with the
24 arthritic process, this study talked about rheumatoid
25 arthritis. The drug has not been approved for rheumatoid

1 arthritis. I think it is being used primarily for
2 osteoarthritis even though I am sure there are patients out
3 there with rheumatoid arthritis that are using the drug, and
4 maybe the postmarketing people can tell us that. But, I
5 think in the context of what we are seeing it is going to
6 have to be the individual judgment of the clinician,
7 weighing the benefits of relieving the pain and the
8 discomfort to the patient versus the risk of cardiovascular
9 events.

10 DR. NISSEN: Very briefly, just a quick correction
11 to Dr. Wolfe's comments, it is really not that myocardial
12 infarction is a sexier disease than upper GI hemorrhage, it
13 is really that cardiologists are sexier than
14 gastroenterologists --

15 [Laughter]

16 -- so just to be clear about that. If there is
17 one thing that we can say for sure, is that aspirin is good.
18 You know, studies like the PPP trial, which was very recent,
19 show once again in a group of people with not very many risk
20 factors -- just had that one risk factor including age,
21 there was a striking reduction in cardiovascular morbidity
22 and mortality when you give aspirin. So, you know, probably
23 a lot more people ought to be on aspirin than are on aspirin
24 and I think that is a general public awareness issue.

25 I don't think we can give guidance here because we

1 just don't know. So, the best we can hope for is the
2 statement that says something like what Dr. Pina said, which
3 is that clinicians must weigh the cardioprotective
4 advantages of aspirin with the potential concomitant risk of
5 increasing GI hemorrhage when these agents are combined
6 because we don't have hard data to say anything beyond that.
7 We just don't know. But let's not forget that aspirin is a
8 good thing for people. I think, unfortunately, it is good
9 for the heart and not so good for the stomach, and that is a
10 really big problem.

11 MS. MCBRAIR: I do feel that there aren't studies
12 warranting any great change in what we say, other than that
13 it is the clinician's decision as to how best to proceed. I
14 do think we need additional studies.

15 DR. WOFSY: A couple of quick points, first and
16 maybe foremost, I have been aware for years that
17 cardiologists and gastroenterologists were richer than
18 rheumatologists but I am disturbed to find out that they are
19 also sexier.

20 [Laughter]

21 Just a couple of quick points. I agree that the
22 labeling already says what is accurate about aspirin and
23 doesn't need to be changed. In a few moments, I am sure we
24 will discuss the sponsor's claim that they have shown a
25 benefit with respect to GI complications with their drug in

1 people who are not on aspirin. And, if we concur with that
2 conclusion, then absolutely the next question with regard to
3 the GI tract is, is that benefit undermined by concurrent
4 use of aspirin in people where it is indicated? So, that is
5 going to be an important question to answer, assuming we
6 accept the claim that has been put before us.

7 DR. CALLAHAN: In answering this specific
8 question, I agree with what Dr. Cryer said, that we don't
9 have any more information to warrant changing what is
10 already in the label.

11 DR. HARRIS: I am persuaded by what Dr. Cryer
12 said. I mean, there is something already in the warning
13 label. I think the worry I have is again the issue that a
14 number of patients who could be potentially on this drug are
15 probably going to be the sorts of patients one wants to put
16 on aspirin, and the question is what does one do with that,
17 given that we have no data with respect to the combination
18 of Vioxx and low dose aspirin that we can rely on. I
19 actually leave to the FDA to decide exactly how they will
20 deal with wording that.

21 DR. WILLIAMS: My bias prior to coming to this
22 meeting was that if you added aspirin to a specific COX-2
23 inhibitor you eliminated the unique benefits of the specific
24 COX-2 inhibitor. I have heard nothing in the last two days
25 that would change that bias. So, if they wish to change

1 that bias they need to do additional studies.

2 DR. SAMPSON: Obviously there is nothing in the
3 data in VIGOR that allows us to make a conclusion about
4 aspirin and Vioxx. Further studies warranted? Clearly,
5 yes. I just want to throw in a reminder. Yesterday, when
6 we looked at the CLASS study and we added aspirin to
7 ibuprofen we got this paradoxical result and maybe a data
8 anomaly, but there was something that people should be aware
9 of.

10 DR. ELASHOFF: Clearly, to address this question
11 we need additional data.

12 DR. HARRELL: Just on one comment you made, Allan,
13 I think we have to remember that aspirin in the study
14 yesterday means cardiovascular risk factors as much as it
15 means taking aspirin. But I would suggest we need
16 additional studies and I would just remind everybody, as
17 though you didn't already know, that a single 2 X 2
18 factorial study is worth more than two two-arm studies.

19 DR. PINA: I would like to add one caveat to the
20 clinician that we are trying to give some advice to, to
21 remind them that these effects may be incremental the longer
22 the patient is on the drug, even though we are certain, and
23 that the doses used in the VIGOR study were higher than the
24 doses that would be ordinarily used in practice and that, in
25 fact, have been approved for osteoarthritis. So, we are

1 dealing with higher doses and perhaps longer duration of
2 drug administration than may be used in practice.

3 DR. HARRIS: I am not going around the table with
4 respect to are additional studies warranted, but yesterday
5 we did see the combination to some degree, of Celebrex and
6 low dose aspirin, the question is when one asks are
7 additional studies warranted specifically with respect to
8 rofecoxib, whether or not there is a sense that additional
9 studies or what is there already is sufficient. So, I will
10 ask for a show of hands this time with respect to the
11 question I raised, which is are additional studies required
12 with respect to rofecoxib and low dose aspirin as stated
13 here? I am going to ask whether or not we could have a show
14 of hands, yes or no.

15 DR. WILLIAMS: The problem is that there are
16 always new studies warranted, and that is the comment that
17 Dr. Wofsy made earlier and I think we can always say that.
18 I think that we have data now. Unless they want to change
19 the fact that aspirin eliminates the benefit, I don't think
20 there are additional studies needed. If they wish to show
21 that they are beneficial in the face of aspirin, they would
22 need to do additional studies.

23 DR. HARRIS: That is a no. Are there any yes's?

24 [Show of hands]

25 MS REEDY: Seven.

1 DR. HARRIS: Are there no's?

2 DR. WOFSY: If you are defining Dr. Williams'
3 comment as consistent with a no, I am a no. If you are
4 asking would I like that information, I am a yes.

5 DR. HARRIS: Remember, all we are doing is
6 providing guidance so we take it in that spirit.

7 I want to go to the third question, considering
8 the results of the VIGOR trial, do the current NSAID-related
9 target organs for toxicity in the current NSAID template
10 remain applicable? In parentheses there is GI, renal/fluid
11 retention, hepatic and skin. Please discuss. I will open
12 for discussion.

13 DR. WOLFE: I am comment only on the GI because
14 that is what I am here for. I am a firm believer in setting
15 forth the hypothesis, designing a study appropriately,
16 checking the results, and if the results match your
17 hypothesis your primary goal has been achieved. I think the
18 data both presented by Merck and by the FDA show that there
19 is, indeed, a decreased risk of GI toxicity associated with
20 the use of this drug. No matter what arguments can be made
21 about, well, was it because of naproxen being the comparator
22 -- I don't know. The study was designed. It was approved
23 by the FDA. I think we have to go with what the results
24 showed. I think in that regard I have to say that there is
25 decreased risk of GI events. Endoscopically as well as

1 outcomes show a parallel decrease in the rate of GI
2 complications.

3 DR. HARRIS: Could I take it that by saying so you
4 are saying the results, with respect to naproxen, are
5 generalizable to other non-steroidals?

6 DR. WOLFE: No, you can't say that but, on the
7 other hand, this is one of the difficulties of yesterday.
8 Until the FDA establishes recommendations or guidelines for
9 these studies we have no choice because otherwise you can
10 come and say, well, that one didn't show it so you can
11 change the label because it could be that they are safe for
12 other drugs. The burden of proof has been achieved as far
13 as I am concerned. There was a study which was designed;
14 the hypothesis was tested; the results actually warrant a
15 change, I think, in the label saying that the studies done
16 to date show a decreased risk of upper gastrointestinal
17 hemorrhage and ulceration.

18 DR. WILLIAMS: I agree with Dr. Wolfe that I think
19 they have met the burden of proof. Now, I don't think a
20 single comparison is generalizable to all NSAIDs but I think
21 they do have to change the label to say that in the one
22 study that was done it was shown to make a difference. As
23 opposed to the other three systems that were mentioned here,
24 I don't think there is anything to suggest that anything
25 needs to be changed in that part of the label.

1 DR. HARRIS: Can I make a comment before you do,
2 Dr. Elashoff? Could we then say that we could make a
3 similar remark with respect to Celebrex versus ibuprofen
4 because, of course, there was an advantage there?

5 DR. WOLFE: I will respond to that. Again, you
6 have a primary goal. You have a hypothesis. You have an
7 objective. If you meet the objective statistically -- you
8 have ground rules. FDA has ground rules. Don't you have
9 ground rules? And, if the ground rules show -- studies are
10 not designed in a vacuum. They are designed with your
11 input. If the goal is achieved, then you can say what the
12 goal was and what it showed. If you don't show it, you
13 can't say it.

14 DR. ELASHOFF: I don't see any reason to change
15 what is said with respect to the GI. This was only one
16 NSAID. The rate was about 2 percent, and what is stated on
17 the template is a rate of 2-4 percent. So, that is
18 consistent with that rate. As I said yesterday, there is no
19 evidence that some purported advantage to this shows up as
20 an overall advantage to the patient because, in fact, there
21 is a significantly higher overall adverse event rate for
22 this drug. So, I don't see any reason for changing the GI
23 template.

24 DR. WILLIAMS: In response to your previous
25 question to Dr. Wolfe and me, I would agree that with

1 Celebrex you could report that it also showed a benefit
2 opposed to ibuprofen. You could also say that there was no
3 benefit when compared to diclofenac because you have data on
4 both drugs.

5 DR. NISSEN: Well, I am just a poor cardiologist
6 so I don't have a lot of sophistication about the GI tract,
7 but it seems to me that we can't make this like it is in the
8 Olympics. When you pole vault, you know, you go over a
9 height and then somebody comes around and says, "well, okay,
10 you made that height; we're going to put another bar up for
11 you to go over." I mean, it seems to me the sponsor here
12 did a very large, probably pretty expensive study, with the
13 advice and consent of the FDA. They created this template
14 of goals. They made those goals very clear from the very
15 beginning. They achieved not a marginal amount of
16 statistical significance on the GI side but an unequivocal
17 statistical significance. So, the statement that rofecoxib
18 is safer, from the gastrointestinal point of view, with
19 respect to the endpoints that were used over naproxen is a
20 fact, in my view, and not a marginal one, and I think that
21 should be reflected in the product literature.

22 So, just as I think there is uncertainty on the
23 cardiovascular side, I think you can't keep raising the bar
24 here forever. I think at some point you have to say this is
25 proven, and I was convinced by the data. We can't say

1 anything about other comparators, nor should we, but I think
2 we can state as a fact, or it can be stated in the product
3 literature that in a large comparative trial, compared to
4 naproxen, there was enhanced GI safety.

5 DR. WOFSY: I don't think the public is well
6 served if we approach this discussion on what I view, to
7 some extent, as technicalities even though they come close
8 to my heart because they are technicalities that rest on the
9 scientific method and statistical significance.

10 Let me explain what I mean by that. Yesterday we
11 saw a study that didn't risk to statistical significance
12 with respect to the primary endpoint, and today we saw one
13 that did, and my view is that to distinguish between them,
14 frankly, would be a technicality and would not be a service
15 to the public.

16 Let me explain, therefore, what I think we have
17 learned in part from the last two days and in part from
18 before the last two days. I made some notes this morning
19 and I think they run through all the comments that have been
20 made. All NSAIDs are not created equal. They exist on a
21 continuum where benefits in one area may come at the cost of
22 complications in another area. And, the results of studies
23 as a result may well depend on which one you choose to
24 compare to, where it is on that continuum. Just to use two
25 medications that aren't before us, for example, diclofenac

1 may have less GI adverse effects than some and be less
2 cardioprotective, and ibuprofen or Naprosyn may have more GI
3 side effects than some and be more cardioprotective.

4 I think that is the message that is emerging. I
5 think the other part of the message that is emerging is that
6 the COX-2 inhibitors exist on that continuum. They exist at
7 one extreme of that continuum but they exist on that
8 continuum. And, I have been convinced by this morning's
9 data that, at least with respect to some of the other non-
10 steroidal on that continuum, they have less GI toxicity. I
11 also have been concerned that that reduction in GI toxicity
12 may come at a high cost in terms of complications elsewhere.

13 From a labeling point of view, it seems to me it
14 would be indefensible not to share that information with the
15 public, both pieces of that information. I haven't seen a
16 single thing in the two days from one of these drugs that
17 would contradict things that have been presented in the
18 opposite presentation and so I would hesitate to use a
19 technicality to somehow deal with them differently. It just
20 flies in the face of my understanding of the data that has
21 been presented and my understanding of the science that is
22 at the base of the data.

23 So, from a labeling point of view, I think it is
24 frankly clear what we have learned from these studies. It
25 is important what we have learned from these studies, and it

1 ought to be shared, I think, in the sense that I have tried
2 to describe it.

3 Just going one step beyond since the comments I
4 have made speak to the value of what has been done, I should
5 also say that what I have just said is from a labeling
6 standpoint. From a patient standpoint, I think there are
7 very serious questions raised about whether patients who
8 take these drugs would be better served by a
9 cardioprotective traditional NSAID unless they are at high
10 risk for ulcer disease. I am not suggesting that going into
11 the label but I am just pointing out that depending on
12 exactly what you are thinking here and where you are going,
13 you could frame this in different ways. But from a labeling
14 point of view, we have learned some things and they should
15 be shared.

16 DR. SAMPSON: I agree with you. There is apparent
17 large variation in the NSAIDs. I don't know how that is
18 going to be played out in terms of the labeling by the Food
19 and Drug Administration, but in terms of Dr. Nissen's
20 comment, if we do stick to the technical labeling it would
21 seem to me, as part of that statement about the beneficial
22 effects, you would want to put in something that it was
23 shown only in an RA population and make that very clear, and
24 also that no aspirin was taken and the benefit is very
25 restricted both in population and in the adjunctive use of

1 aspirin.

2 DR. PINA: I have been going through the labeling
3 template that we have in front of us, and under warnings
4 there is this whole list of gastrointestinal warnings.
5 There is a list about anaphylactoid pregnancy, hepatic,
6 renal, hematologic, asthma, fluid retention, edema and there
7 is no cardiac. The cardiac is tucked back here where
8 additional adverse experiences have been reported. So, I
9 think this warrants a paragraph up here, sooner rather than
10 at the bottom, about the observations made in this trial
11 about the risk of thrombotic events.

12 Now, having said that, I agree that the sponsor
13 has proven what they meant to prove in a restricted
14 population of rheumatoid arthritis patients who had no
15 aspirin. And, I think any way you turn around that data
16 versus naproxen, it is very restrictive. I agree with what
17 Allan said. What they set out to prove in a very restricted
18 population is true and I think the public needs to know
19 that. At the same time, I want to see the paragraph about
20 the cardiac events. Then the rest, as we normally do, we
21 have to leave to the clinician to make the decision.

22 DR. HARRIS: Let me interpose at this point that,
23 in fact, the issue of the cardiac events and whether or not
24 that should be included is something that I think is worth a
25 word or two. But I really would like to settle the GI

1 events. In other words, the question is should there be a
2 change to the template.

3 I wonder if I might get a chance to make a comment
4 and then we can keep going, for what it is worth. But, you
5 know, I must say that there are, from my perspective, non-
6 steroidal and non-steroidal, and there is clearly a
7 spectrum of GI toxicities. Had yesterday, and I hate saying
8 so, the choice been ibuprofen and naproxen instead of
9 ibuprofen and diclofenac, I guess the sense would have been
10 something very different. And, today, had it been that the
11 sponsors decided to choose naproxen and diclofenac then,
12 because we saw a meta-analysis, by the way, where diclofenac
13 looked like it came in at about the same level as rofecoxib
14 -- and I think there is, indeed, a general question that Dr.
15 Wolfe raised today and it has been bothering me because on
16 the warning label you are really making a statement in
17 comparison to all non-steroidal, and that makes the
18 assumption, with respect to GI toxicity, that they are alike
19 and perhaps they are not.

20 So, really we can't go back and redo these studies
21 today but the issue is in the future when one is designing
22 studies like this what advice should be given in terms of
23 comparator drugs because, again, we are struggling with the
24 issue and we will continue to struggle with the issue. You
25 know, which drug is best representative of the non-

1 steroidals? Is it one? Is it two? Is it three? It goes
2 on and on, and I think it is very bothersome and very
3 different for us to make a decision here.

4 DR. DELAP: I think my immediate reaction to the
5 last thing you were saying as to choosing which drug to
6 compare to, and that has been a theme of some of the
7 comments, I kind of hate to say it but the reality is we
8 would probably come back to you and ask you what you think
9 is the drug that we should be comparing to so that we can
10 tell our sponsors and have some public discussion of that.

11 DR. HARRIS: I will agree with that.

12 DR. NISSEN: Nigel, I hear what you are saying --
13 what would have happened; what could have happened had the
14 CLASS study used a different comparator, but we don't have
15 that. We have what we have, and the comparators that were
16 chosen are the ones that were chosen for whatever reasons
17 they were chosen.

18 Let me ask a rhetorical question. Are we going to
19 ask the sponsors of these drugs to go do 8000-patient
20 studies for each of the dozen or so potential comparators
21 before we agree that there is some benefit? It is not going
22 to happen. It is not reasonable to make it happen and,
23 therefore, we have to tell people what we know.

24 Let me tell you that I learned a lot today as a
25 cardiologist, a lot about the GI tract that I didn't know

1 before, and what, of course, is going on here is what Dr.
2 Wofsy refers to as clinical judgment. You know, I actually
3 prescribe these agents to cardiovascular patients so now
4 what I am likely to do, and what I would like to share with
5 our community is a knowledge base that says that if you have
6 a patient that is at low risk for cardiovascular events, a
7 younger person perhaps without co-morbidities, they may be
8 better served by an agent that has better GI protective
9 effects, that is, is less likely to result in GI morbidity.
10 If I have a patient who has had four prior myocardial
11 infarctions and a couple of episodes of unstable angina, I
12 am going to think twice about giving them a COX-2 inhibitor
13 certainly without aspirin.

14 So, the real question for us is how do we
15 communicate the message from the trials that we have heard
16 in a fair, balanced way that allows a clinician to weigh the
17 risks and benefits of the classes of drugs available to them
18 and choose a drug that, in their hearts and their conscience,
19 is the best drug for that individual patient? So, I favor
20 statements of facts in the labeling as we know them. I like
21 the way you, Allan, revised my comments about what do we
22 know. We know that for this population the naproxen event
23 rates in the GI tract were higher than they were for
24 rofecoxib, and we know that cardiovascular event rates were
25 higher for rofecoxib than they were for the comparator.

1 So, I think that what we really need to do is to
2 provide some kind of a balanced view of what the studies
3 showed and then let the physicians use their clinical
4 judgment to pick the agents that they think make the most
5 sense for their individual patients. Beyond that we can't
6 guess at what another comparator would have shown because we
7 don't have that data and we are not likely to have it in the
8 near future or even at any time in the future.

9 DR. ZEGER: I agree with your point that what we
10 really have to do is think about what evidence is available.
11 What I don't hear being talked about at all is the evidence
12 that came from careful analysis of the OA population and to
13 compare it to what we have learned in the RA population in
14 this trial and if I could just very quickly for the
15 committee --

16 DR. HARRIS: I am going to have to say no. I am
17 sorry but I am going to have to say no.

18 DR. ZEGER: Let me just conclude that what I see
19 there is a relative risk with a diverse set of comparators
20 of 0.54 or 0.45 in the OA population and a relative risk of
21 0.46 in the RA population for a different comparator. So, I
22 think when you think about what is the presentation of
23 evidence, it is important to think about all the studies
24 that have been done and not to dismiss some because they
25 were done through a series of trials rather than just one

1 trial.

2 DR. HARRIS: What I am going to ask now is whether
3 or not, in your opinion as I am going around the room, you
4 believe the warning label should be changed with respect to
5 GI toxicity. Keep your remarks brief, please, because I
6 think most of you have had an opportunity to make a
7 statement. It really is mostly yes or no in a quick way.
8 Dr. Cryer, though you are not a voting member, let the
9 record show that I am going to start with you.

10 DR. CRYER: Thank you, Dr. Harris. One of the
11 things that I have actually learned from this body of
12 literature and this process, and I think one of the things I
13 actually feel strongly about with respect to informing the
14 consumer is that there is a continuum with regard to NSAID
15 toxicity. I think if you are going to make labeling changes
16 that needs to be a very clear message that gets relayed to
17 prescribers and to consumers because I absolutely agree with
18 you, it is not just NSAIDs as a group. All NSAIDs aren't
19 the same. So, the continuum message clearly needs to be in
20 there.

21 But I actually also fall in agreement with my
22 colleague here, Dr. Wolfe, and that is that with respect to
23 these labeling considerations what drives the label is a
24 process, a process that you define ahead of time, and there
25 are rules that are inherent in that process that drives the

1 label. So, I personally don't really see these issues as
2 technicalities because you have to have a process and rules
3 that actually drive what ultimately goes into a label. So,
4 the two points in terms of how I see it are that there is a
5 continuum issue and I think you are obligated to put in the
6 label the results you have with respect to the studies that
7 you have designed based upon prespecified rules.

8 DR. WOLFE: I don't want to be repetitive but I am
9 a little disturbed. Again, there are rules and the rules
10 are established and if you play by the rules, then you are
11 rewarded if you are able to meet your primary objective. I
12 feel very strongly about this, if you are going to mention
13 the cardiovascular warnings in there because you found some
14 potential cardiovascular effects and you don't mention the
15 fact that there was a protective effect on the GI tract, I
16 think you are being remiss because you are misguiding people
17 to say there may be a drug out there that doesn't cause
18 ulcerations much. So, I really think if you are going to do
19 one you have to do the other. If you are not going to do
20 one, then don't do the other.

21 DR. PINA: We are addressing right now the GI
22 effects.

23 DR. HARRIS: Absolutely.

24 DR. PINA: I have read the section on the
25 warnings. The section on the warnings looked pretty narrow

1 to me and I don't think there isn't anything here that isn't
2 a fact, including that patients who have a prior history of
3 ulcer disease are more prone to have spontaneous bleeding
4 with these drugs. I don't think there is anything in here
5 that is any different since it is generic for NSAIDs.

6 I would add, however, a statement such as in so
7 many patients with rheumatoid arthritis Vioxx has shown
8 such-and-such a reduction in GI events without concomitant
9 use of aspirin at doses of such-and-such -- just a statement
10 stating exactly what was proven here. The rest is very
11 generic and is valuable information that I think clinicians
12 should read because that applies to non-steroidals, period.

13 DR. NISSEN: I would change the label. Again, the
14 term that has been used about the study is that there is a
15 technicality involved. To me, a properly designed,
16 prospective, blinded, randomized study with a strong p value
17 can't be viewed as a technicality. So, for that comparator
18 in that population there is very strong evidence and,
19 therefore, the labeling should reflect the strong evidence
20 that is available. Beyond that, I can't say anything else.

21 MS. MCBRAIR: I think the label should reflect
22 exactly what we know and what we learned from the study that
23 was done.

24 DR. WOFSY: I had hoped to just say yes but I also
25 have to sort of regret my own choice of the word

1 technicality, which has deflected some of this discussion
2 because I don't believe I meant technicality in the sense
3 that it has been interpreted.

4 I just think the following, yes, I think the label
5 should be changed to reflect -- and I am not sure or where,
6 to reflect the proven advantage demonstrated with respect to
7 GI toxicity in this study and to reflect the concerns that
8 have been raised about what price may be paid for that
9 advantage.

10 What I meant to imply by technicality, and I will
11 just comment on it now but that will obviously be the FDA's
12 decision, I wouldn't know how to implement this myself, is
13 that I would think it would be a disservice if what came out
14 of the discussion for the last two days was somehow to imply
15 to the community that there is a difference between the
16 agents we have talked about. There is a difference in what
17 has been proven in some statistical sense, but I have not
18 heard a single thing that would lead me to believe, as a
19 clinician, that I have strong evidence that there is a
20 fundamental difference either in efficacy or toxicity. How
21 that is reflected when you go to write it, that is your
22 problem and not mine. And, that is really all I meant by
23 technicality.

24 DR. CALLAHAN: I agree with what Dr. Cryer said
25 about the continuum. I do think that is an important issue