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ARTHRITIS ADVISORY COMMITTEE

NDA # 21-042/S007, Vioxx (Rofecoxib, Merck)

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## C O N T E N T S

Call to Order and Introduction, E. Nigel Harris, M.D.	4
Meeting Statement, Kathleen Reedy	
Merck Research Laboratories Presentation:	
Introduction, Bonnie J. Goldmann, M.D.	5
COX-2 Selectivity and Previous Clinical Safety Data, Alan Nies, M.D.	10
VIGOR Study and Related Clinical Data, Alise Reicin, M.D.	26
FDA Presentation:	
Medical Overview, Maria Lourdes Villalba, M.D.	95
Gastrointestinal Review, Lawrence Goldkind, M.D.	100
Cardiovascular Review, Shari L. Targum, M.D.	109
Statistical Review, Qian Li, Ph.D.	112
Summary, Maria Lourdes Villalba, M.D.	116
Open Public Hearing:	
Sidney M. Wolfe, M.D.	141
Discussion and Questions:	
Vioxx Questions	147
General Questions	215

## 1 P R O C E E D I N G S

2 **Call to Order and Introductions**

3 MS. REEDY: Good morning and welcome to day two of  
4 the Arthritis Advisory Committee meeting. Again, thank you  
5 very much to our committee members for their generosity of  
6 time and sharing of their expertise in this important  
7 deliberation.

8 Drug safety is a cooperative effort involving  
9 manufacturers, public health providers and patients.  
10 Clearly, the goal is the optimizing through careful study to  
11 provide information that guides the right drug to the right  
12 patient at the right time. The study we will hear about  
13 today represents a significant effort and further  
14 characterization of a drug safety profile, in this instance  
15 rofecoxib. We look forward to today's deliberation and,  
16 again, thank you and welcome.

17 DR. HARRIS: The next item on the agenda is the  
18 presentation by Merck Research Laboratories. I want, as I  
19 did yesterday, to give Merck every opportunity to present  
20 their data. Since there will be discussions this afternoon,  
21 I am going to ask members of the committee to ask for  
22 questions of clarification but to save further discussion  
23 for this afternoon. Dr. Bonnie Goldmann?

24 **Merck Research Laboratories Presentation**25 **Introduction**

1 DR. GOLDMANN: Good morning. Mr. Chairman,  
2 members of the advisory committee, FDA, ladies and  
3 gentlemen, I am Dr. Bonnie Goldmann, from the Department of  
4 Regulatory Affairs, Merck Research Laboratories.

5 [Slide]

6 I would like to thank the advisory committee and  
7 FDA for the opportunity to present Merck's landmark Vioxx  
8 gastrointestinal outcomes research trial. VIGOR, which  
9 definitively confirm, extend and generalize the  
10 gastrointestinal safety of rofecoxib, Merck's selective  
11 inhibitor of the cyclooxygenase enzyme COX-2. These results  
12 involve an array of hard clinical GI endpoints that confirm  
13 the GI safety results of our original NDA, now in a  
14 different disease population.

15 We believe these highly significant results merit  
16 modification of our product label to reflect a more  
17 appropriate presentation of the demonstrated GI safety that  
18 is specific to rofecoxib.

19 [Slide]

20 As you know, the cyclooxygenase family of enzymes  
21 are central to the metabolic conversion of arachidonic acid  
22 to a number of prostanoids. COX-1 is constitutively  
23 expressed in a number of tissues, and is responsible for  
24 maintenance of gastric glucosal integrity, normal platelet  
25 function and participates in several aspects of renal

1 function, most notably regulation of salt and water  
2 regulation. COX-2 is the isoform induced at sites of  
3 inflammation and injury, and more recently has also been  
4 shown to have a constitutive role in renal salt and water  
5 balance.

6           Conventional non-selective NSAIDs, which during  
7 these presentations will be referred to simply as NSAIDs,  
8 inhibit both COX-1 and COX-2. As a result, they provide an  
9 anti-inflammatory and analgesic effect but, as a class, non-  
10 selective NSAIDs also affect renal handling of salt and  
11 water, impaired gastric mucosal integrity and inhibit normal  
12 platelet aggregation.

13           [Slide]

14           NSAID gastropathy leads to serious upper GI side  
15 effects, one of the most common serious drug-related adverse  
16 events associated with non-selective NSAIDs. Based on  
17 extrapolations from the ARAMIS database, it has been  
18 estimated that NSAID gastropathy results in approximately  
19 100,000 hospitalizations and 16,500 deaths per year.

20           [Slide]

21           With this serious problem of non-selective NSAIDs  
22 in mind, we embarked on the development of selective COX-2  
23 inhibitors based on the premise that selective inhibition  
24 would retain the anti-inflammatory and analgesic properties  
25 of NSAIDs. Renal salt and water effects would also be

1 retained, at least in part, but COX-1-related functions in  
2 the gastric mucosa and platelets should be unaffected.

3 [Slide]

4 These predictions were crystallized in what has  
5 been called the COX-2 hypothesis. The hypothesis proposes  
6 that a selective COX-2 inhibitor should demonstrate anti-  
7 inflammatory and analgesic efficacy similar to non-selective  
8 NSAIDs, significantly improved GI safety compared to non-  
9 selective NSAIDs, effects on renal sodium handling similar  
10 to NSAIDs and no inhibitory effect on platelets.

11 [Slide]

12 The original NDA for rofecoxib, which was  
13 discussed with this committee in April, 1999, confirmed this  
14 hypothesis in patients with osteoarthritis and acute pain.  
15 Based on that data, FDA approved rofecoxib for the following  
16 indications: Vioxx is currently indicated for the relief of  
17 signs and symptoms of osteoarthritis, management of acute  
18 pain in adults, and treatment of primary dysmenorrhea. The  
19 recommended chronic dose for osteoarthritis is 12.5-25 mg  
20 per day, and for acute pain the short-term dose is 50 mg per  
21 day. Based on the previously published results from our  
22 Phase IIb rheumatoid arthritis efficacy study and the  
23 recently completed Phase III efficacy studies that have not  
24 yet been submitted to the FDA, we will be proposing 25 mg  
25 per day as a recommended dose for rheumatoid arthritis.

1 [Slide]

2 Rofecoxib is now available in 74 countries, and  
3 since its initial marketing in mid-1999 it is estimated that  
4 approximately 13 million patients have taken the drug in the  
5 U.S. and more than 24 million worldwide. Total exposure now  
6 exceeds 4 million patient years and, to this date, the  
7 general safety and tolerability profile of rofecoxib seen in  
8 postmarketing surveillance is consistent with the profile  
9 defined in the original NDA.

10 [Slide]

11 Today, we are here to discuss the VIGOR study.  
12 This single, large, multi-center, active comparator  
13 controlled trial of clinical outcomes in patients with  
14 rheumatoid arthritis was designed in consultation with  
15 regulatory agencies, including the FDA, to demonstrate the  
16 GI safety of rofecoxib based on clinically important GI  
17 events. In response to the agency's recommended, the dose  
18 of rofecoxib used in this study was twice the maximum  
19 recommended chronic dose for patients with osteoarthritis  
20 and rheumatoid arthritis. A subsequent speaker will discuss  
21 the rationale for dose selection in more detail.

22 [Slide]

23 As we shall describe today, and in conformance  
24 with the predictions of the COX-2 hypothesis, the results of  
25 VIGOR further established the clinical meaningful

1 enhancement of GI safety for rofecoxib over non-selective  
2 NSAIDs, measured by significant clinical upper GI events  
3 with no effects on platelet function and minor effects on  
4 renal sodium excretion that are already reflected in the  
5 current product labeling for rofecoxib.

6 [Slide]

7 The agenda for today's Merck presentation is as  
8 follows: Dr. Nies will review the COX-2 selectivity of  
9 rofecoxib and the clinical data that set the stage for  
10 VIGOR. Dr. Reicin will then review the VIGOR results and  
11 put the study in the context of related clinical data, all  
12 of which broadly validate the COX-2 hypothesis.

13 The advisory committee members have previously  
14 received a background package from Merck that summarizes the  
15 large body of information in more detail than time allows us  
16 to discuss here this morning.

17 [Slide]

18 In addition to our speakers, Merck has brought  
19 several consultants to the meeting. These experts are  
20 available to facilitate the advisory committee's discussions  
21 and deliberations. Dr. Gerald Appel, Dr. Claire Bombardier,  
22 Dr. Christopher Hawkey, Dr. Marc Hochberg, Dr. Loren Laine,  
23 Dr. Marvin Konstam, Dr. John Oates, Dr. James Neaton, Dr.  
24 Walter Peterson and Dr. Scott Zeger.

25 I would now like to turn the podium over to Dr.

1 Nies.

2 **COX-2 Selective and Previous Clinical Safety Data**

3 DR. NIES: Good morning.

4 [Slide]

5 I am Dr. Alan Nies, in the Department of Clinical  
6 Sciences at Merck Research Laboratories.

7 [Slide]

8 I would like to review today some of the aspects  
9 of our development program to serve as a background for the  
10 VIGOR results that you will be hearing about.

11 [Slide]

12 We began the program with the hypothesis as  
13 outlined by Dr. Goldmann and that you heard about yesterday.  
14 We expected that a COX-2 selective inhibitor that did not  
15 have effects on COX-1, like rofecoxib, would demonstrate  
16 only a subset of the properties that were well-known with  
17 the NSAIDs. Thus, we expected that the efficacy would be  
18 equivalent to the NSAIDs but there would be differences in  
19 the safety profile and, in particular, there would be an  
20 improved safety profile in the gastrointestinal tract.

21 Today I will review the studies that showed the  
22 selective for COX-2 for rofecoxib, and I would like to talk  
23 about three special safety issues -- gastrointestinal safety  
24 which set the stage for the VIGOR trial, renal safety and  
25 cardiovascular safety. I will not be spending any time

1 looking at the efficacy of the drug. This was well reviewed  
2 in the original NDA with this committee, jut to remind you  
3 that the doses that are approved for chronic use are 12.5 mg  
4 and 25 mg a day for osteoarthritis. As has been mentioned,  
5 our recently completed Phase III studies in rheumatoid  
6 arthritis indicate that 25 mg is the maximally effective  
7 dose in this disease as well.

8 [Slide]

9 Just one slide on the efficacy in osteoarthritis  
10 shown in this graph. This is a one-year study comparing  
11 rofecoxib to diclofenac. Patients come in, at this time are  
12 screened, and after they meet the screening criteria they  
13 are withdrawn from their NSAIDs and they flare. They are  
14 randomized at this point, here, and then they are continued  
15 on one of the three arms through the period of the trial.

16 As you can see, with pain on this axis, more pain  
17 is higher on the axis and all three treatments, 12.5 mg, 25  
18 mg of rofecoxib and diclofenac 50 mg 3 times a say, are  
19 similar over the period of this year and the effect is  
20 maintained.

21 [Slide]

22 We defined selectivity in three major ways in this  
23 trial. First was assays using whole blood, and this assay I  
24 think is well familiar to many on this committee as a way to  
25 look at selectivity in patients or volunteers receiving the

1 drug. Secondly, we looked at bleeding time and platelet  
2 function and, thirdly, we looked at the effect on  
3 cyclooxygenase activity in gastric mucosal biopsies of  
4 volunteers who were receiving the drug.

5 First with the whole blood assay, we did not find  
6 any effects of rofecoxib on COX-1 at any dose that we  
7 studied, and these doses were as high as 1000 mg single  
8 doses, and 375 mg multiple doses over a period of a couple  
9 of weeks, and with none of those regimens did we see any  
10 effect on COX-1. These doses, as you can appreciate, are  
11 much higher than the clinical doses of 12.5 and 25.

12 We did find, however, over the dose range that is  
13 used clinically that there was a dose-dependent inhibition  
14 of COX-2. This inhibition was similar to that seen with the  
15 NSAIDs. So, at a clinically effective dose of rofecoxib,  
16 one has inhibition of this whole blood assay of COX-2 at the  
17 25 mg dose, for instance, at about 60-80 percent inhibition  
18 and that is the same degree of inhibition one sees with  
19 drugs such as diclofenac and ibuprofen used at their high  
20 clinical doses.

21 [Slide]

22 The dose-dependent effects of rofecoxib are  
23 consistent with its linear pharmacokinetics. This just  
24 shows the area under the curve, shown on this side, versus  
25 dose. You can see the linearity. Area under the curve is a

1 way to look at exposure of the drug. It is the curve on  
2 concentration versus time. You can see that this goes up  
3 linearly with dose. This is independent of food and is  
4 consistent across age groups, and such consistency and  
5 linearity is not seen with all drugs, as you are probably  
6 aware.

7 [Slide]

8 Secondly, we looked at the effects on bleeding  
9 time and platelet function as a way to look at COX  
10 selectivity. Rofecoxib does not affect bleeding time or  
11 platelet aggregation. For the bleeding time we studied  
12 doses up to 375 mg, multiple doses. Here, shown on the  
13 left, is placebo, 250, 375. I think it is evident that  
14 there is no effect of the drug on bleeding time.

15 We studied platelet aggregation at the dose of 50  
16 mg and we did not see any effect of rofecoxib on inhibiting  
17 platelet aggregation. Inhibition is shown as an increase on  
18 this axis.

19 You can see the effects of aspirin. Aspirin at 81  
20 mg, which is the so-called low dose aspirin for  
21 cardioprotective reasons, inhibits platelet aggregation 90  
22 percent or so, and that is shown on this slide. It is  
23 really the gold standard for what one needs to achieve to  
24 get platelet function inhibited for cardiac protection.

25 [Slide]

1           The last thing that we looked at for selectivity  
2 was the assays of cyclooxygenase in gastric mucosal  
3 biopsies. We originally showed to this committee, back in  
4 '99, some data that was developed for 25 mg of rofecoxib and  
5 that was included in our NDA. Today I will show you data  
6 with a higher dose, 50 mg.

7           [Slide]

8           The way the study was done, the individuals took  
9 the drugs for 5 days, and then 4 hours after their last dose  
10 they were endoscoped and had gastric mucosal biopsies. The  
11 ability of that biopsy tissue to generate prostaglandins was  
12 used as an index of the synthetic capacity in the COX  
13 activity. Since the gastric mucosa normally only contains  
14 COX-1, this is really another way of looking at COX-1.

15           On the left are shown the effects naproxen 500 mg  
16 twice a day. We see the expected effect of naproxen to  
17 reduce the ability of the mucosa to produce prostaglandins.  
18 On the right is shown rofecoxib 50 mg a day. This is the  
19 high dose that we used in VIGOR, twice our maximum dose on  
20 the market, and it did not have an effect. This is similar  
21 to the results that we had seen at 25 mg.

22           [Slide]

23           I would now like to turn to selective aspects of  
24 the safety. First I will review some of the GI special  
25 studies that were done and were submitted in our NDA as this

1 sets the groundwork for VIGOR. I will then go through some  
2 renal and cardiovascular issues.

3 [Slide]

4 We did two sets of endoscopic studies during the  
5 NDA development. The first was a study in normal subjects.  
6 This was done early in the program, really before we had an  
7 idea of what our dose would be. So, we chose a dose of 250  
8 mg of rofecoxib and gave this for a week to normal  
9 volunteers. They were endoscoped at the beginning and the  
10 end of that week. This was compared with a dose of aspirin  
11 of 650 mg 4 times a day and ibuprofen 800 mg 3 times a day  
12 in separate groups. At the end of the week we found that  
13 the 250 mg of the rofecoxib, which is really an order of  
14 magnitude higher than our clinical dose, was far superior to  
15 the aspirin and the ibuprofen. There was also a placebo  
16 group in this and the results were close to placebo with our  
17 drug.

18 We then did some studies with osteoarthritis  
19 patients. We did to replicative studies there. We looked  
20 at 25 mg and 50 mg of the rofecoxib and we compared it in  
21 this study to ibuprofen 800 mg 3 times a day. This went on  
22 for 6 months. We also had a placebo group for 4 months.  
23 The endoscopies were done at baseline, at 6 weeks, at 12  
24 weeks and then at 6 months.

25 [Slide]

1           The data from these studies that we have shown to  
2 this committee previously, and these data are in our label,  
3 are shown here. These are the two studies. There was a  
4 U.S. study and a multinational study. The 12 week and 24  
5 week endoscopies are shown on each side, and this is the  
6 cumulative incidence rate of gastroduodenal ulcers. The  
7 placebo is only in the 12 week because it was discontinued  
8 after that time point.

9           I think it is clear that ibuprofen, shown here, in  
10 these two studies, causes a large number of ulcers over this  
11 period of time and that rofecoxib at both doses is markedly  
12 superior to ibuprofen in both studies, and at the 12-week  
13 time point you can see how it compares to placebo.

14                     [Slide]

15           The last of the special GI safety studies that we  
16 did was to look at the entire GI tract. This was done in  
17 sort of an indirect way. First we looked at fecal blood  
18 cell loss. We injected radio labeled red cells and looked  
19 at the excretion in the feces. We also looked at the  
20 absorption of normally non-absorbable EDTA as an index of  
21 how the drugs altered intestinal permeability. The  
22 comparators in these trials included ibuprofen at the doses  
23 I talked about before, 800 3 times a day, and indomethacin,  
24 50 mg 3 times a day.

25                     In both of these trials the 25 mg and 50 mg dose

1 of rofecoxib was superior to NSAIDs, and in both of these  
2 trials they were also statistically equivalent to placebo.

3 [Slide]

4 I would now like to move on to the renal aspects  
5 of COX-2 inhibition.

6 [Slide]

7 It is well-known that prostaglandins have effects  
8 in the kidney. Both COX-1 and COX-2 are present in the normal  
9 kidney. This wasn't apparent early on when we started but  
10 it became apparent fairly early, that COX-2 is present in  
11 mammalian kidney. We do know that prostaglandins are  
12 involved in renal physiology. They are involved in control  
13 of glomerular filtration rate, in control of renin  
14 secretion, and they have effects on sodium, potassium and  
15 water homeostasis. It is well-known that NSAIDs produce a  
16 small incidence of edema and hypertension.

17 [Slide]

18 Throughout our development program, it has become  
19 clear that the COX-2 selective inhibitors are equivalent to  
20 the non-selective NSAIDs in many of their renal effects and  
21 particularly in reducing the urinary sodium excretion. This  
22 does appear to be dose related. For instance, the 12.5 mg  
23 of rofecoxib appears to have less of this effect than 25 and  
24 50 mg.

25 [Slide]

1           Shown in this slide are some data from a recently  
2 completed study looking at an NSAID, naproxen 500 mg twice a  
3 day, rofecoxib 25 mg a day, celecoxib 200 mg twice a day.  
4 These are the highest approved doses for the COX-2  
5 inhibitors and a medium dose for naproxen but a usually used  
6 dose of naproxen.

7           On this axis, the Y axis, is the change from  
8 baseline in daily urinary sodium excretion. This is a study  
9 that was done in 60-80 year old patients who were brought  
10 into sodium balance on a metabolic ward. They were on a  
11 normal to high sodium diet, 200 mEq of sodium per day. At  
12 baseline they were started on one of these four regimens.  
13 As you can see, the effects occurred over this period of  
14 time, and almost all of the action occurs within the first  
15 two or three days where there is an inhibition of sodium  
16 excretion or sodium retention occurring, which then comes  
17 back into balance after three days and is maintained over  
18 the 14-day period.

19           The statistical hypothesis was that rofecoxib and  
20 celecoxib would be similar, and we had defined similarity  
21 bounds for that and the study showed, indeed, that the drugs  
22 were similar. In fact, they were similar to naproxen, and  
23 all of these were different than the placebo.

24           [Slide]

25           I would next like to turn to the cardiovascular

1 issues. I know that that is of great interest and  
2 importance to the committee and to us, particularly as it  
3 relates to the platelet-endothelium interactions.

4 [Slide]

5 I would like to just review briefly a little bit  
6 about the biochemistry. Some of this was reviewed yesterday  
7 as well. Platelets contain only COX-1 and this produces  
8 thromboxane A-2. Thromboxane A-2 promotes platelet  
9 aggregation, and that is important for normal hemostasis.  
10 But, it can also be a pathological problem. For instance,  
11 in the setting of atherosclerosis with a ruptured plaque,  
12 platelets aggregate and can occlude the vessel, producing an  
13 occluding thrombus.

14 Non-selective NSAIDs and aspirin can inhibit COX-  
15 1. If they do this sufficiently or enough, this can produce  
16 a change in platelet aggregation. Now, this can be  
17 protective against the thrombus production that is  
18 pathologic but it also interferes with normal hemostasis.  
19 So, in the studies that are done with anti-platelet drugs  
20 frequently there is some excess bleeding and often it is  
21 seen in minor bleeding episodes such as epistaxis and  
22 ecchymosis.

23 In order to have a sufficient effect on  
24 thromboxane to really have an effect on platelet  
25 aggregation, one has to inhibit thromboxane production by

1 greater than 90 percent. Aspirin certainly does this  
2 because of its mechanism-based irreversible inhibition of  
3 COX-1. Some of the NSAIDs also have this potential.

4 [Slide]

5 I would like to show you some data that were  
6 generated during our NDA process, submitted in the NDA, on  
7 various NSAIDs that we used in our program, both in the  
8 VIGOR program and in our Phase IIb/III program on platelet  
9 aggregation.

10 On this axis is the amount of inhibition of  
11 platelet aggregation, and various drugs are listed along  
12 here. You can see that placebo and rofecoxib has no effect  
13 on platelet aggregation. Aspirin, as the gold standard, has  
14 this 90 percent or more inhibition. Then, the other NSAIDs  
15 are arrayed along here, naproxen, ibuprofen and diclofenac.

16 I would like to focus on these two, ibuprofen and  
17 naproxen, which look as if they may provide a substantial  
18 degree of platelet inhibition.

19 [Slide]

20 To do that over a time course, this is what we  
21 see. This study looks over a dosing interval with naproxen,  
22 ibuprofen and placebo. This is at steady state so the zero  
23 time point is the end of the previous dosing interval. So,  
24 for naproxen that is 12 hours after a dose; for ibuprofen it  
25 is 8 hours after a dose. Then we measured it for the next 8

1 hours. Naproxen, as you can see, maintains over this period  
2 of time a 90 percent inhibition of platelet aggregation,  
3 whereas ibuprofen, because of its short half-life  
4 presumably, does not have a sustained effect and in order to  
5 have complete cardioprotection from this mechanism one has  
6 to sustain that effect over the full time that patients are  
7 taking the drug. Ibuprofen, at least as given in this  
8 regimen of 800 mg 3 times a day, does not do that, whereas  
9 naproxen 500 mg twice a day does do that.

10 [Slide]

11 Just to compare naproxen and aspirin effects in  
12 kind of a numeric say here to give you an impression of how  
13 close they are, the mean inhibition from baseline with  
14 aspirin is 92; 93 with naproxen. The medians are the same  
15 and the range is the same. So, I think from the mechanistic  
16 point of view one can see that naproxen does have the  
17 potential for producing effects that are like aspirin.

18 [Slide]

19 So, this raises the question can some NSAIDs, such  
20 as naproxen, have aspirin-like cardioprotective properties  
21 by potently inhibiting platelet aggregation? In thinking  
22 about this question over the past few months, we have  
23 developed both some animal data and some epidemiologic data  
24 that supports this, and this will be mentioned again by Dr.  
25 Reicin in the next talk.

1 [Slide]

2 Returning to the platelet-endothelium interface,  
3 on the other side of the issue we have the endothelium. The  
4 endothelial cell is really a lot harder to study than the  
5 platelet. It is not easy to isolate and it is a much more  
6 complicated cell than the platelet. The endothelium, in  
7 terms of the prostanoid that it produces it is largely  
8 prostacyclin. This inhibits platelet aggregation, and is  
9 thought to be important for the balance between these two.

10 The cyclooxygenase responsible for prostacyclin  
11 product has classically been thought to be COX-1, as was  
12 mentioned yesterday. If you take out vascular tissue and  
13 look at endothelial cells, look at immunohistochemistry, you  
14 really only find COX-1. So, it was really a surprise when,  
15 during our development program, even in what were normal  
16 volunteers it was found that the drugs rofecoxib and  
17 celecoxib reduced the urinary excretion of a metabolite of  
18 prostacyclin.

19 Although we don't know the cells that produce the  
20 prostacyclin that result in this metabolite coming out in  
21 the urine, this implied that these drugs had an effect on  
22 synthesis of prostacyclin and the implication is that the  
23 endothelial cell is part of that and, so, COX-2 must be  
24 involved in the endothelial cell. This means then that the  
25 non-selective NSAIDs, as well as the COX-2 inhibitors, have

1 the potential for reducing prostacyclin production.

2 [Slide]

3 This show the two studies that I was referring to.  
4 These were both done at the University of Pennsylvania but  
5 they were two separate studies. On the left is a study with  
6 celecoxib single dose treatment 400 mg versus ibuprofen.  
7 This is data 6 hours after dose. Urinary excretion of the  
8 metabolite of prostacyclin -- this metabolite, urinary 2,3  
9 dinor-6-keto-PGF-1alpha, is usually in the literature called  
10 PGIM, and you can see the effect of placebo here and then  
11 the effects of the two drugs on the excretion, which is on  
12 this axis. With rofecoxib 2 weeks of therapy at 50 mg a  
13 day, a similar effect.

14 [Slide]

15 These effects indicate that the COX-2 selective  
16 inhibitors reduce by about 60 percent potentially the  
17 reduction in systemic prostacyclin synthesis. We don't know  
18 what the importance of a 60 percent reduction is on this  
19 side of the issue. We do know it takes 90 percent  
20 inhibition on this side in order to see an effect. I think  
21 the data are even more hard to interpret because the  
22 endothelial cell also produces other potent anti-platelet  
23 factors. The best known of these and the most well studied,  
24 at least recently, is nitric oxide, and this is produced  
25 independent of the cyclooxygenase system. So, this

1 redundancy in the system I think makes interpretation of the  
2 60 percent reduction of one part of it hard. Nonetheless, I  
3 think this raises the issue as to what is the clinical  
4 importance of inhibiting system prostacyclin synthesis  
5 without inhibiting platelet aggregation.

6 [Slide]

7 Because of these two questions, we were  
8 sufficiently concerned that there might be an alteration in  
9 the balance that first we examined our Phase IIb/III  
10 database carefully to see whether there was any evidence of  
11 excess cardiovascular events. Just to remind you that the  
12 comparators there were ibuprofen 800 mg three times a day,  
13 diclofenac 50 mg three times a day -- those two drugs  
14 probably do not maintain sustained suppression of platelet  
15 aggregation. We did not see any signal in our Phase IIb/III  
16 database. But we decided that the most rigorous way that we  
17 could look at this was to establish a standard operating  
18 procedure to capture and adjudicate all cardiovascular  
19 events in all future COX-2 inhibitor trials, not just with  
20 rofecoxib but with subsequent entries to the market that we  
21 would be studying, and that was set up in 1988. This was  
22 prior to VIGOR and actually we set that up prior even to  
23 putting in the initial NDA.

24 [Slide]

25 Just to conclude this introductory talk, rofecoxib

1 is a COX-2 inhibitor without effects on COX-1 at and above  
2 the clinical doses.

3 Rofecoxib 12.5 mg and 25 mg once daily is equally  
4 effective to NSAIDs in osteoarthritis and, as I have  
5 mentioned, 25 mg is the maximally effective dose in  
6 rheumatoid arthritis, as we have recently seen in our Phase  
7 III data but these have not yet been reviewed by the agency.  
8 Rofecoxib's effects on the gastrointestinal mucosa are  
9 significantly less than the NSAIDs. The renal effects of  
10 the COX-2 inhibitors are similar to the NSAIDs.

11 Platelet thromboxane production is variably  
12 reduced by the NSAIDs; not all of them produce effects that  
13 would be important here but some do. But the COX-2  
14 inhibitors have no effect on this and that I think is very  
15 important. And, systemic prostacyclin synthesis is reduced  
16 by both.

17 This really summarizes the COX-2 hypothesis then  
18 that the clinical effects that we have seen are really a  
19 consequence of its selective inhibition of COX-2 and its  
20 lack of effect on COX-1, and this supports the initial  
21 hypothesis.

22 I would now like to introduce Dr. Alise Reicin,  
23 who will discuss with you the details and the findings of  
24 the VIGOR trial.

25 **VIGOR Study and Related Clinical Data**

1 DR. REICIN: Dr. Nies has just presented to you  
2 the background behind the COX-2 hypothesis, and I will be  
3 discussing with you today the clinical profile of rofecoxib  
4 which was developed on the basis of that hypothesis.

5 [Slide]

6 I am going to begin my discussion with a review of  
7 studies and analyses that were done to determine if  
8 rofecoxib was associated with a clinically important  
9 reduction in clinically important GI outcomes. The focus of  
10 that discussion will be the results of the recently  
11 completed large GI outcomes study done in patients with  
12 rheumatoid arthritis, and I will refer to this study as the  
13 VIGOR study.

14 I will also be reviewing with you the results of  
15 our prespecified analysis on clinical upper GI events with  
16 our Phase IIb/III OA studies. The results of this analysis  
17 were previously presented to this committee in 1999.

18 I will then have a brief review of efficacy  
19 measurements in the VIGOR study, followed by a review of  
20 general safety and cardiovascular safety. Again, for these  
21 latter two topics the focus will be VIGOR but in the context  
22 of the overall development program.

23 [Slide]

24 As Dr. Nies discussed, as a part of the Phase III  
25 Vioxx development program, a series of studies were

1 performed which evaluated the effect of rofecoxib compared  
2 to non-selective NSAIDs as markers of NSAID-induced GI  
3 toxicity. These studies, which included surveillance  
4 endoscopy studies and studies which evaluated subclinical GI  
5 blood loss, clearly demonstrated the improved GI safety  
6 profile of rofecoxib but it was important to determine  
7 whether the results of those studies could be translated  
8 into a reduction in clinically important GI outcomes, the  
9 type of outcomes that are important to patients and to  
10 physicians who are caring for those patients.

11 I think, as you will see today, we have in fact  
12 demonstrated that these endoscopy studies were predictive.  
13 We have now demonstrated a significant reduction in  
14 clinically important upper GI events in rofecoxib compared  
15 to non-selective NSAIDs in patients with RA in the VIGOR  
16 study and also in patients with osteoarthritis in our  
17 combined Phase IIb/III OA analysis.

18 [Slide]

19 The primary and secondary endpoints for the study  
20 were defined in collaboration with the FDA. The primary  
21 endpoints were what I will refer to as clinical upper GI  
22 events. In the past they have been known as PUBs, and these  
23 include gastroduodenal perforations, symptomatic  
24 gastroduodenal ulcers, ulcers which are rarely complicated  
25 by gastric outlet obstruction, and upper GI bleeding.

1           When I am talking about symptomatic ulcers, we are  
2 specifically referring to ulcers that were picked up because  
3 patients presented with signs or symptoms for which an  
4 investigator initiated a workup. We were very careful  
5 during our studies not to have an algorithm for  
6 investigators to use but, instead, to encourage them to make  
7 decisions about whether to initiate a workup based on the  
8 decisions they would make in their medical practice.

9           A subgroup of these events I will refer to as  
10 complicated upper GI events. These are more severe. These  
11 are the type of events for which patients often present to  
12 in an emergency room for urgent evaluation. They include  
13 gastroduodenal perforations, obstructions, and a subgroup of  
14 the upper GI bleeds which I will refer to as major upper GI  
15 bleeds. These are bleeds that are associated with the need  
16 for a blood transfusion, evidence of volume depletion or a  
17 two gram or more drop in hemoglobin.

18                   [Slide]

19           In both the Phase IIb/III OA analysis as well as  
20 in the RA outcome study a process was established for the  
21 review and adjudication of clinically important GI events by  
22 an outside panel of experts. Their process started with the  
23 blinded investigators who evaluated and then reported  
24 suspected clinical events. Endpoint packages were then put  
25 together which included source documents, as well as a

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1 narrative, and these were sent to an independent blinded  
2 adjudication panel who reviewed the source documents and,  
3 based on prespecified stringent case definitions, classified  
4 the events as confirmed or unconfirmed and complicated or  
5 uncomplicated.

6 [Slide]

7 We will now switch to the VIGOR study. VIGOR was  
8 a multinational study. It was conducted in 301 clinical  
9 centers in 22 countries and on five continents. There were  
10 three major external committees which oversaw the conduct of  
11 the study. The first was the blinded endpoint adjudication  
12 committee, and I have already reviewed with you the function  
13 of that committee. In addition, there was a blinded  
14 steering committee, in essence an oversight committee. This  
15 committee was charged with the overall scientific and  
16 operational direction for the study. They reviewed and  
17 approved the original protocol as well as all protocol  
18 amendments. Lastly, there was an independent data safety  
19 and monitoring board who reviewed interim safety analyses  
20 and, based on the results of those analyses, could request  
21 modifications in the protocol or early termination of the  
22 study to ensure patient safety. However, no such requests  
23 were made during the conduct of the study.

24 [Slide]

25 There were several prespecified objectives for the

1 VIGOR study. The primary objective was to demonstrate that  
2 rofecoxib at twice the maximum chronic dose would be  
3 associated with a significant reduction in confirmed  
4 clinical upper GI events. So, our primary endpoints were  
5 events, clinical upper GI events that were confirmed by the  
6 adjudication committee. In addition, there were several  
7 secondary objectives and they were to demonstrate a  
8 significant reduction, in rofecoxib compared to naproxen, of  
9 confirmed complicated upper GI events, confirmed plus  
10 unconfirmed clinical upper GI events and confirmed plus  
11 unconfirmed complicated upper GI events.

12 Most of the literature on NSAID-related GI  
13 bleeding relates to GI bleeds from the upper GI tract.  
14 However, there are some epidemiologic studies which suggest  
15 that patients who take non-selective NSAIDs are also at an  
16 increased risk from lower GI bleeding and, therefore, we  
17 also had an exploratory objective to demonstrate a reduction  
18 in all episodes of clinical GI bleeding. This means GI  
19 bleeding from either the lower or the upper GI tract. I am  
20 not here talking about asymptomatic drops in hemoglobin. We  
21 are talking about clinical GI bleeds that were reported by  
22 investigators.

23 [Slide]

24 Why did we choose to study patients with  
25 rheumatoid arthritis instead of patients with

1 osteoarthritis, or potentially a combination of the two?  
2 Well, as has been shown to this panel previously and I will  
3 again show you today, the improved GI safety with rofecoxib  
4 was previously demonstrated in patients with OA in our  
5 combined upper GI event analysis. Therefore, the steering  
6 committee raised potential ethical concerns about  
7 essentially repeating the same experiment in the same  
8 patient population.

9           On the other hand, patients with rheumatoid  
10 arthritis are routinely treated with chronic NSAIDs, and  
11 this is a patient population that is known to be at high  
12 risk for NSAID-related events. Lastly, the use of RA  
13 patients would allow us to both confirm the results of the  
14 Phase IIb/III GI safety analysis, as well as to extend those  
15 results to a completely different patient population and,  
16 therefore, would extend the generalizability of the results.

17           [Slide]

18           In our Phase IIb/III OA studies the main NSAID  
19 comparators were diclofenac and ibuprofen. Naproxen was  
20 chosen for this study because, first of all, in the U.S. and  
21 many other countries it is the most commonly prescribed  
22 NSAID for the treatment of rheumatoid arthritis and, in  
23 addition, it would give us yet another NSAID against which  
24 rofecoxib had been compared. And, 500 b.i.d. was chosen as  
25 the dose because it is the most commonly used dose for the

1 treatment of rheumatoid arthritis.

2 On the other hand, as requested by the FDA, due to  
3 the important issue of dosage creep in clinical practice,  
4 rofecoxib was studied at two times the maximum chronic dose,  
5 50 mg. So, 50 mg is two to four times the dose for  
6 osteoarthritis, and the FDA has questioned in their  
7 background package whether 50 mg would, in fact, be the dose  
8 for the treatment of rheumatoid arthritis. However, the  
9 results of our recently completed Phase IIb and III studies,  
10 which have not yet been reviewed by the agency, confirm that  
11 25 mg is the dose for the treatment of rheumatoid arthritis.  
12 These studies demonstrated that 50 mg did not provide  
13 additional efficacy compared to 25 mg, and both 25 and 50  
14 provided efficacy which was similar to naproxen at 1000 mg  
15 daily. Therefore, by studying the most commonly used dose  
16 of naproxen compared to two times the maximum dose of  
17 rofecoxib would provide rigorous testing of the GI safety of  
18 rofecoxib.

19 [Slide]

20 In VIGOR, over 8000 patients were randomly  
21 assigned to either rofecoxib 50 mg once a day or naproxen  
22 500 b.i.d. in a double-blind manner. Randomization was  
23 stratified by a prior history of a clinical upper GI event.  
24 There was a brief washout of prior NSAID therapy, minimum  
25 three days, which was essentially to ensure pharmacologic

1 separation of prior NSAID therapy with study therapy. This  
2 was not done to elicit a flare in patients' rheumatoid  
3 arthritis as you do in an efficacy study.

4           During the study patients were seen after  
5 randomization at six weeks, four months, every four months  
6 thereafter and then at study termination, and they were  
7 contacted in between clinical visits with frequent telephone  
8 calls.

9           [Slide]

10           The duration of the study was determined both by  
11 time and the cumulative number of endpoints, and the study  
12 was terminated based on prespecified stopping guidelines  
13 which were in the protocol. A minimum of all three of the  
14 following need to have occurred for the study to be  
15 terminated: 120 confirmed clinical upper GI events had to  
16 have occurred; plus, 40 confirmed complicated events; and, a  
17 minimum of six months had to have elapsed since the last  
18 patient was randomized. All of these criteria were, in  
19 fact, met prior to termination of the study. The study was  
20 terminated approximately 13 months after the first patient  
21 was randomized and 8.5 months after the last patient was  
22 randomized.

23           [Slide]

24           In order to be enrolled in the study, patients had  
25 to have a diagnosis of rheumatoid arthritis. They had to be

1 50 years of age or older, or 40 years of age or older if  
2 they were on chronic systemic corticosteroids, and they had  
3 to have been felt by their investigator to require NSAIDs  
4 for at least one year. All patients were tested for occult  
5 blood screening and a positive test resulted in exclusion  
6 from the study. In addition, patients were excluded who  
7 were using medications that might have confounded the GI  
8 safety results of the study. Therefore, patients who were  
9 using aspirin, anticoagulants, anti-platelet agents or anti-  
10 ulcer medications, such as proton pump inhibitors or  
11 misoprostol were excluded. However, over-the-counter doses  
12 of H-2-receptor antagonists were allowed prior to entry and  
13 during the study.

14           Before I move on, I do want to point out that we  
15 did appreciate the importance of the question of whether a  
16 safety advantage would be maintained in patients who were  
17 taking aspirin concomitantly with rofecoxib. However, we  
18 also knew, as Dr. Goldkind pointed out during yesterday's  
19 discussion, that we would not be powered to answer that  
20 question if only 10-20 percent of the patients enrolled in  
21 the study were concomitant users of aspirin. Because, as I  
22 will show you today, endoscopy studies are predictive of GI  
23 outcomes for rofecoxib, we have designed and have ongoing an  
24 endoscopy study which is specifically designed to evaluate  
25 this.

1 [Slide]

2 The mean age of patients in the study was 58,  
3 though patients as old as 88 and 89 were also randomized.  
4 In keeping with the patient's diagnosis of RA, 80 percent of  
5 them were female; 8 percent had a prior history of an upper  
6 GI event; and about 2.5 percent had a prior history of  
7 complicated upper GI event. Systemic corticosteroids were  
8 used by a little over 50 percent of patients and a little  
9 over 40 percent of patients were *H. pylori* positive at  
10 baseline. The mean duration of the patients' rheumatoid  
11 arthritis was approximately 11 years, and about 97 percent  
12 of patients met four or more ACR criteria for the diagnosis  
13 of RA. So we know that, in fact, we did this study in a  
14 rheumatoid arthritis patient population. Methotrexate of  
15 other DMARDs were used in over 80 percent of patients in the  
16 study.

17 [Slide]

18 Over 9500 patients were screened. Over 8000  
19 patients were randomized, and over 71 percent of patients  
20 completed the study, meaning that they remained on study  
21 drug at the time of the study termination. This completion  
22 rate was quite high and, in fact, when the study was  
23 designed it was assumed that there would be a 50 percent  
24 dropout rate based on the previous literature.

25 Of the 29 percent of the patients who prematurely

1 discontinued from the study, the reasons for discontinuation  
2 were similar between the two treatment groups and 16 percent  
3 of patients discontinued for an adverse experience in both  
4 groups, and this does include clinical upper GI events. You  
5 can see low and similar rates of discontinuation for lack of  
6 efficacy.

7 [Slide]

8 The median time that patients were on treatment  
9 was 9 months, but you can see up to a maximum of 13 months  
10 for those patients who were enrolled at the beginning of the  
11 enrollment period. There was almost 1700 patient years on  
12 treatment in both groups, and all patients and all events  
13 were included in all analyses for their entire duration of  
14 time on treatment, plus an additional 14 days, to ensure  
15 that we captured all endpoints potentially related to study  
16 therapy. This is consistent with the intent-to-treat  
17 approach and it means that despite the relatively short  
18 three-day washout period there was no censoring of early  
19 events which may have been related to prior NSAID use.

20 [Slide]

21 During the study, 190 patients had clinical upper  
22 GI events reported by their investigators. Of those 190  
23 patients, 170 [sic] patients had confirmed clinical upper GI  
24 events. These are events that were confirmed by the  
25 adjudication committee. Fifty-three of these patients, of

1 the 177 [sic], had confirmed complicated upper GI events.  
2 As you can see, there were 13 patients with unconfirmed  
3 clinical upper GI events. The majority of these were  
4 patients who had upper GI bleeds and did not have enough  
5 source documentation to meet prespecified stringent case  
6 definitions. During most of my discussion today I will be  
7 concentrating on the confirmed events, however, the results  
8 of confirmed plus unconfirmed events were similar because of  
9 these 13 patients 11 were on naproxen.

10 [Slide]

11 The results of our primary endpoint are presented  
12 on this slide. The vertical axis shows the cumulative  
13 incidence of confirmed clinical upper GI events. Time is on  
14 the horizontal axis. I think you can see there is early  
15 separation of the curves. That separation is maintained  
16 over time. The relative risk of sustaining a confirmed  
17 clinical upper GI event on rofecoxib compared to naproxen  
18 was 0.46, which corresponds to a 54 percent reduction, and  
19 that was highly statistically significant in favor of  
20 rofecoxib, with a p value of less than 0.001.

21 [Slide]

22 The results of the key secondary endpoint,  
23 confirmed complicated upper GI events, are presented here.  
24 I think you can see that the curves look quite similar to  
25 what I just showed you for the primary endpoint. The

sg

1 relative risk of sustaining a confirmed complicated upper GI  
2 event on rofecoxib to naproxen was 0.43. That corresponds  
3 to a 57 percent reduction, again statistically significant  
4 in favor of rofecoxib.

5 [Slide]

6 Another way to look at the data is to compare  
7 across the treatment groups the rates per 100 patient years  
8 for these clinical upper GI events. I am showing here three  
9 of the prespecified endpoints. I have already shown you the  
10 results for confirmed clinical upper GI events and confirmed  
11 complicated upper GI events. The relative risk is shown  
12 above with the 95 percent confidence intervals and, again,  
13 both of those were significant.

14 In addition, over here, on the right, are all  
15 episodes of clinical upper GI bleeding. So, these are GI  
16 bleeds from the upper and the lower GI tract. You can see  
17 here also that the relative risk of sustaining a clinical  
18 upper GI bleed on rofecoxib compared to naproxen was 0.38.  
19 That corresponds to a 62 percent reduction and, again, this  
20 was significant.

21 [Slide]

22 To determine if rofecoxib was associated with  
23 reduced incidence of GI bleeding from both the upper and  
24 lower GI tract, we did some exploratory analyses and broke  
25 this down into upper GI bleeds, major upper GI bleeds and

1 lower GI bleeds. Again, you can see significant reductions  
2 in all of these endpoints. The relative risk of sustaining  
3 an upper GI bleed on rofecoxib was 0.36, corresponding to a  
4 64 percent reduction. The relative risk of sustaining a  
5 major upper GI bleed was 0.37, corresponding to a 63 percent  
6 reduction, and the relative risk of sustaining a lower GI  
7 bleed on rofecoxib compared to naproxen was 0.46,  
8 corresponding to a 54 percent reduction and, again, all were  
9 significant.

10 [Slide]

11 The nature of the events that made up the primary  
12 endpoint are delineated on this slide. As predicted from  
13 the epidemiology, the most common events on naproxen were  
14 gastric ulcers, followed by duodenal ulcers and upper GI  
15 bleeds and all of these were reduced in the rofecoxib group  
16 compared to the naproxen group.

17 [Slide]

18 There were consistent significant reductions in  
19 relative risk on rofecoxib compared to naproxen in all of  
20 our endpoints, as demonstrated on this slide. The orange  
21 diamonds here point to the relative risk of sustaining a GI  
22 endpoint on rofecoxib compared to naproxen. The white lines  
23 show the 95 percent confidence intervals. The diamonds that  
24 fall to the left of 1 favor rofecoxib. The top five rows  
25 are five prespecified endpoints; the bottom three were the

1 three exploratory endpoints and, again, you can see very  
2 similar relative risks. Risk reductions ranged from 54 to  
3 64 percent.

4 [Slide]

5 Several risk factors for clinical upper GI events  
6 are known from the literature. These include age greater  
7 than 65; the use of systemic corticosteroids; a prior  
8 history of a GI event; and evidence of *H. pylori* infection.  
9 The point estimates indicate that there was a numerically  
10 reduced risk of sustaining a confirmed upper GI event on  
11 rofecoxib in both patients with and without each of these  
12 risk factors. The study was not designed nor powered to  
13 achieve significant reductions in each subgroup and yet,  
14 surprisingly, we did demonstrate significance in virtually  
15 all of the subgroups tested.

16 [Slide]

17 We also evaluated low risk patients, and I will  
18 put low risk in quotes here. What I am referring to are  
19 patients who are younger than the age of 65. They are not  
20 *H. pylori* positive. They weren't using systemic  
21 corticosteroids and they didn't have a prior history of a GI  
22 event and you can compare those to patients who had one or  
23 more risk factors.

24 As expected, the overall incidence of events in  
25 this "low risk" group was lower than those who had one or

1 more of these events. As you can see, the rofecoxib group  
2 in particular had a very low incidence, 0.2 percent. But,  
3 importantly, the GI safety advantage of rofecoxib was  
4 maintained both in patients with and without any of these  
5 risk factors. There were significant reductions in both of  
6 these groups, ranging from 51-88 percent.

7 [Slide]

8 I am now going to briefly review for you the  
9 results of our Phase IIb/III prespecified clinical GI events  
10 analysis that was done in patients with osteoarthritis. I  
11 would like to compare those to the results of the VIGOR  
12 study. This prespecified analysis included all of our Phase  
13 IIb/III studies done in patients with osteoarthritis. Over  
14 3000 patients were randomized to rofecoxib in doses which  
15 ranged from 12.5 to 50 mg, with a mean dose of 24.7 mg.

16 We had a combined NSAID comparator group that was  
17 prespecified and included diclofenac, ibuprofen or  
18 nabumetone in over 1500 patients, but really the majority of  
19 the exposure here was to diclofenac and ibuprofen. There  
20 was also a small placebo group of over 500 patients who were  
21 on therapy for up to four months.

22 The primary prespecified endpoint was confirmed  
23 clinical upper GI events, the same primary endpoint that we  
24 had from VIGOR. The secondary endpoint was confirmed and  
25 unconfirmed clinical upper GI events. As I noted earlier,

1 the same adjudication committee from VIGOR was used and the  
2 same process for the adjudication of these upper GI events.

3 There were 55 upper GI events reported in our  
4 Phase IIb/III studies. Of these, 49 were confirmed upper GI  
5 events and there were six unconfirmed events. Similar to  
6 what we saw in VIGOR, all six of these events were  
7 unconfirmed GI bleeds and, in fact, all six were on one of  
8 the NSAIDs.

9 [Slide]

10 Similar to what I showed you for VIGOR, these are  
11 the results of the primary endpoint. This is time to  
12 confirmed clinical upper GI events. The relative risk for  
13 sustaining a confirmed upper GI event on rofecoxib compared  
14 to the combined NSAID comparators was 0.45; 55 percent  
15 reduction, statistically significant in favor of rofecoxib.

16 I am not going to show you the results of the  
17 secondary endpoint of confirmed plus unconfirmed events, but  
18 when you add in those six events that were on the NSAID  
19 comparators the relative risk is 0.35, corresponding to a 65  
20 percent reduction and, again, significant in favor of  
21 rofecoxib.

22 [Slide]

23 Although we have limited data on placebo,  
24 comparisons are of interest and since placebo patients were  
25 only treated for a maximum of four months, we performed a

1 four-month analysis. The rate per 100 patient years of  
2 confirmed clinical upper GI events -- I think you can see  
3 the number of events overall is quite small, but the rates  
4 are similar on placebo and rofecoxib and less than the  
5 combined NSAID group.

6 [Slide]

7 Lastly, this represents a side-by-side comparison  
8 of the rates of confirmed clinical upper GI events per 100  
9 patient years from the OA Phase IIb/III studies, on the  
10 left, and from the VIGOR study in patients with rheumatoid  
11 arthritis, on the right. The relative risk reductions are  
12 above them. What you can see is that the relative risk in  
13 the OA studies is 0.45 compared to 0.46 in the rheumatoid  
14 arthritis studies. Therefore, despite the fact that the  
15 patient populations were different -- one was in OA and one  
16 was in RA -- despite the fact that the NSAID comparators  
17 were different -- one was a single study, one was multiple  
18 studies and this one had multiple doses and the VIGOR study  
19 was at the 50 mg dose -- the results were highly and  
20 surprisingly consistent.

21 [Slide]

22 Before I conclude the GI safety section of the  
23 talk, I want to take a moment to review a prespecified  
24 analysis done to examine the overall GI tolerability of  
25 rofecoxib. As you know, NSAIDs are commonly associated with

1 GI symptoms. The etiology of these symptoms really is  
2 unknown and the correlation with mucosal injury is quite  
3 poor. However, these symptoms are important because they  
4 often result in the need to discontinue treatment with non-  
5 selective NSAIDs. In fact, in VIGOR the five most common  
6 reasons for discontinuing from the study, aside from gastric  
7 ulcers, were GI symptoms, such as dyspepsia and epigastric  
8 discomfort.

9           As illustrated in this slide, in both the Phase  
10 IIb/III OA studies, over on the left, and in VIGOR there was  
11 a significant reduction in discontinuations due to GI and  
12 abdominal adverse experiences on rofecoxib compared to the  
13 NSAID group.

14           [Slide]

15           In summary, rofecoxib significantly decreased the  
16 risk of clinically important GI events, in both our Phase  
17 IIb/III OA analysis and in VIGOR, by 54-65 percent. We have  
18 demonstrated consistent and significant effects in all  
19 prespecified endpoints and consistent effects in both high  
20 and low risk subgroups. The improved GI safety has been  
21 demonstrated independently in both OA and RA, and we believe  
22 that these data warrant modification to the current  
23 rofecoxib label to distinguish the GI safety profile of  
24 rofecoxib compared to non-selective NSAIDs.

25           [Slide]

1 VIGOR was designed specifically to test the GI  
2 safety of rofecoxib and not to demonstrate its efficacy in  
3 patients with rheumatoid arthritis. However, to ensure that  
4 the GI safety comparison in VIGOR was not done at a dose of  
5 rofecoxib which was sub-therapeutic compared to naproxen,  
6 four efficacy measurements were included in the study.

7 [Slide]

8 The study employed a non-flare design to monitor  
9 symptomatic stability rather than improvements from  
10 baseline, and the efficacy objective was to assess RA  
11 disease activity during treatment with rofecoxib versus  
12 naproxen using standard efficacy measurements, which  
13 included a patient global assessment of disease activity, an  
14 investigator global assessment of disease activity, the  
15 percent of patients who discontinued due to lack of efficacy  
16 and then, at the request of the FDA, we also included the  
17 modified health assessment questionnaire, which is in  
18 essence a disability questionnaire.

19 [Slide]

20 Efficacy was virtually identical in both treatment  
21 groups in all endpoints measured. The top three rows show  
22 you the changes from baseline in the three questionnaires.  
23 Negative values are consistent with improvements. Despite  
24 the fact that we didn't have a flare, there were small and  
25 similar improvements in both treatment groups, and

1 discontinuations due to lack of efficacy occurred at a low  
2 incidence and a similar rate in the two treatment groups.

3 [Slide]

4 Therefore, in VIGOR rofecoxib and naproxen  
5 demonstrated similar efficacy in the treatment of RA, and  
6 this is consistent with our Phase IIb/III data which  
7 demonstrated that both 25 and 50 mg of rofecoxib had  
8 efficacy which was similar to 1000 mg a day and, again, the  
9 agency has not yet reviewed those studies.

10 [Slide]

11 I am now going to turn to a review of rofecoxib's  
12 general safety. As I discuss this, I think it is important  
13 to remember that the study was designed specifically as a GI  
14 safety study and not a general safety study and, therefore,  
15 the dose of rofecoxib studied was two times the maximum  
16 chronic dose.

17 [Slide]

18 However, at that dose the safety profile of  
19 rofecoxib demonstrated similar efficacy to what we saw in  
20 our Phase IIb/III program and, therefore, is consistent with  
21 current labeling. In the Phase IIb/III studies rofecoxib  
22 was generally well tolerated, as I showed you already;  
23 demonstrated a superior GI tolerability compared with non-  
24 selective NSAIDs.

25 In addition, as you would expect, based on the

1 effects of COX-2 inhibition on renal sodium handling, the  
2 incidence of renal vascular adverse experiences, such as  
3 edema and hypertension, were similar to NSAIDs within the  
4 clinical dose range at 12.5 and 25 mg. At 50 mg, which is  
5 two times the maximum dose, there is an increase in these  
6 adverse experiences. This increase is reflected in our  
7 current labeling and is not unexpected since these adverse  
8 experiences are dose-related for NSAIDs and, as you increase  
9 the dose from 25 to 50 mg, you do get a doubling in systemic  
10 exposure since rofecoxib has dose proportional kinetics  
11 within this dose range. Lastly, rofecoxib, like other  
12 NSAIDs, is associated with a low incidence of increased  
13 transaminases. It occurs in about 0.5 to 1 percent of  
14 patients. The incidence of these increases in the Phase III  
15 studies was similar to ibuprofen and significantly less than  
16 diclofenac.

17 [Slide]

18 The next two slides are going to give you a high  
19 level overview of clinical and laboratory adverse  
20 experiences reported in VIGOR. This will be followed by a  
21 series of slides which explore in greater detail specific  
22 safety issues of interest. Statistical testing was done  
23 only on adverse experience analyses which were prespecified  
24 and, therefore, throughout general safety discussions p  
25 values will only be shown for predefined safety analyses.

1 In VIGOR the overall incidence of clinical AEs,  
2 drug-related AEs and discontinuations due to AEs were  
3 similar in the two treatment groups. There was a small  
4 difference, which was statistically significant, in serious  
5 adverse experiences with rofecoxib having slightly more than  
6 naproxen. This did not carry over to serious drug-related  
7 adverse experiences which were, in fact, high on naproxen  
8 compared to rofecoxib. I will be discussing these during  
9 the cardiovascular part of my talk.

10 [Slide]

11 Overall, the incidence of laboratory adverse  
12 experiences was low, occurring in approximately 10 percent  
13 of patients. Serious AEs and discontinuations for lab AEs,  
14 again, were low and with similar rates in the two treatment  
15 groups.

16 [Slide]

17 Prespecified adverse experiences were chosen based  
18 on the known safety profile of NSAIDs and COX-2 inhibitors,  
19 and these AEs included AEs related to GI tolerability, renal  
20 sodium handling, renal function and hepatic function.  
21 Discontinuations due to these adverse experiences were  
22 generally prespecified as the primary approach to analyze  
23 the clinical importance of these adverse experiences. This  
24 slide summarizes the results of these analyses.

25 Statistical testing was done on all of these

1 adverse experiences and significant reductions were seen for  
2 only two of them, discontinuations due to digestive system  
3 AEs, which I have shown you, which was in favor of  
4 rofecoxib, and discontinuations due to hypertension related  
5 AEs, which was in favor of naproxen. Discontinuations due  
6 to edema related AEs, all AEs of congestive heart failure,  
7 discontinuations due to renal related AEs and  
8 discontinuations due to hepatic AEs were not significantly  
9 different between the two treatment groups.

10 [Slide]

11 In this slide and in the next several slides the  
12 crude incidence of specific AEs is shown in the hatched bars  
13 and discontinuations due to these AEs is shown in the solid  
14 bars. On the left are the results of our Phase IIb/III OA  
15 studies, and on the right are the results from VIGOR. By  
16 showing the results of our Phase IIb/III OA studies and  
17 VIGOR side by side, I am not trying to make direct  
18 statistical comparisons. Rather, the results of the Phase  
19 IIb/III studies are provided to determine whether the VIGOR  
20 results were generally consistent with current labeling.

21 Edema can occasionally be associated with NSAIDs  
22 and COX-2 inhibitors. Usually these AEs are minor clinical  
23 importance. They often resolve without a change in  
24 medication, and only rarely do they lead to discontinuation  
25 of the study drug. I am showing you here lower extremity

1 edema because in our database the majority of edema-related  
2 AEs are reported as lower extremity edema, and lower  
3 extremity edema is the AE that is reflected in our label.

4           In the Phase IIb/III studies, as you can see, the  
5 12.5 and 25 mg dose the incidence was similar to the NSAID  
6 comparators. Discontinuation rates in all doses were  
7 unusual but there was a dose-related increase at the 50 mg  
8 dose. The results of VIGOR were similar to what was seen in  
9 our Phase IIb/III studies and although the overall incidence  
10 of these AEs was actually slightly less than in the Phase  
11 IIb/III studies, despite the longer duration of VIGOR, it  
12 was, as you can see, slightly higher than the naproxen group  
13 and discontinuations were also numerically higher than  
14 naproxen but did not reach statistical significance.

15           [Slide]

16           This slide illustrates the incidence of  
17 hypertensive adverse experiences and, again, in the Phase  
18 IIb/III studies at 12.5 and 25 mg the incidence was similar  
19 to that seen with the NSAID comparators. There was an  
20 increase at the 50 mg dose; similarly in VIGOR, at 50 mg,  
21 two times our maximum dose, higher incidence compared to a  
22 commonly used dose of naproxen, likely related to the dose  
23 disparity between those. Discontinuations were also greater  
24 on rofecoxib, although at a low rate, 0.7 percent, compared  
25 to naproxen and this did reach statistical significance.

1 [Slide]

2 The effects of COX-2 inhibition on renal sodium  
3 handling can rarely lead to congestive heart failure, and in  
4 both our Phase IIb/III OA studies and in VIGOR there was a  
5 low incidence of these events. The majority of these events  
6 did not lead to discontinuation of the study drug. In fact,  
7 in our Phase IIb/III OA studies there were really so few  
8 events that in order to make any sort of meaningful  
9 comparisons we have combined the rofecoxib and the NSAID  
10 groups here. You can see, in fact, that numerically there  
11 was a greater incidence of CHF adverse experiences in the  
12 combined NSAID group. This did not reach statistical  
13 significance. In VIGOR there was a numerically greater  
14 incidence of congestive heart failure incidence but, again,  
15 overall quite low, about 4 percent compared with naproxen  
16 which was about 2.2 percent.

17 [Slide]

18 NSAIDs can rarely cause deterioration in renal or  
19 hepatic function, and to evaluate these potential adverse  
20 differences we evaluated discontinuations due to related  
21 AEs, as well as changes in renal or liver chemistries which  
22 fell outside predefined limits of change. Discontinuations  
23 related to renal function or hepatic function occurred at a  
24 low incidence and were similar between the two groups.  
25 There was one death in the naproxen group due to hepatic

1 failure and, in fact, that patient was considered a  
2 completer and is not counted in this analysis.

3 [Slide]

4 The predefined limits of change analyzed in this  
5 study included patients with lab changes on two consecutive  
6 occasions or on one occasion and associated with  
7 discontinuation. The predefined limits of changes for serum  
8 creatinine was an increase of 0.5 mg/dL from baseline and  
9 more than the upper limit of normal, and the increases in  
10 ALT -- the predefined limits were equal to or more than  
11 three times the upper limit of normal. As you can see, the  
12 percent of patients meeting these predefined limits of  
13 change was quite low in both treatment groups.

14 [Slide]

15 In summary, the VIGOR general safety results were  
16 similar to the results from our Phase IIb/III studies.  
17 Overall, rofecoxib was generally well tolerated and  
18 demonstrated a superior GI tolerability compared with non-  
19 selective NSAIDs.

20 The incidence of adverse experiences related to  
21 sodium retention, such as edema and hypertension, are  
22 similar to NSAIDs within the clinical dose range. However,  
23 these adverse experiences are dose related, and with dosages  
24 above our maximum chronic dose there is an increase in  
25 these. Discontinuations at any dose, however, are rare and

1 adverse experiences related to a decrease in renal function  
2 as well are rare and similar to NSAIDs.

3           Increases in liver function tests in patients on  
4 rofecoxib are similar to naproxen and ibuprofen and lower  
5 than those seen with diclofenac.

6           [Slide]

7           The one area where VIGOR demonstrated results  
8 which were different than those seen in the Phase IIb/III  
9 studies was in cardiovascular safety. When I refer to  
10 cardiovascular safety I am specifically referring to the  
11 incidence of thrombotic events, such as myocardial  
12 infarctions and cerebral vascular accidents. This is  
13 separate and distinct from renal-related AEs, such as edema  
14 and hypertension which were just reviewed and are dose-  
15 related, mechanism-dependent side effects.

16           [Slide]

17           Before I present the VIGOR cardiovascular results  
18 I want to take a moment to review with you the data that Dr.  
19 Nies previously presented to you on the effects of NSAIDs  
20 and selective COX-2 inhibitors on thromboxane and  
21 prostacyclin formation, and the questions that these data  
22 raised.

23           First, as you know, aspirin is an irreversible  
24 inhibitor of COX-1 and mediates near complete inhibition of  
25 platelet aggregation throughout its entire dosing interval.

1 While all non-selective NSAIDs inhibit platelet aggregation,  
2 most non-selective NSAIDs do not produce sustained  
3 inhibition of platelet aggregation. Naproxen, however, does  
4 inhibit platelet aggregation by about 90 percent throughout  
5 its entire dosing interval, and the magnitude of that effect  
6 is similar to that seen with aspirin. On the other hand,  
7 COX-2 selective inhibitors do not inhibit platelet  
8 aggregation. Both non-selective NSAIDs and COX-2 inhibitors  
9 do reduce secretion of urinary metabolite prostacyclin by  
10 40-70 percent and the clinical significance of this is not  
11 known.

12 [Slide]

13 This data raises the following question, by  
14 inhibiting platelet function, can some NSAIDs have aspirin-  
15 like cardioprotective properties and would you expect there  
16 to be differences between the NSAIDs based on the ratio of  
17 COX-1 to COX-2 inhibition in the pharmacokinetics of the  
18 drugs? On the other hand, what are the clinical  
19 implications of inhibition of systemic prostacyclin  
20 synthesis without anti-platelet activity?

21 To address these issues, a standard operating  
22 procedure was established after the completion of the Phase  
23 IIb/III OA studies and prior to VIGOR to capture and  
24 adjudicate cardiovascular events in all COX-2 inhibitor  
25 studies.

1 [Slide]

2 Just as I did for you with the GI events, I just  
3 want to take a moment to review the definitions of some of  
4 the cardiovascular endpoints that I will be referring to.  
5 Again, these are thrombotic serious cardiovascular events.  
6 The first are confirmed thrombotic cardiovascular events.  
7 So, these are events that were confirmed as being thrombotic  
8 events by a blinded cardiovascular adjudication committee,  
9 and they include events such as myocardial infarctions,  
10 strokes, transient ischemic attacks, unstable angina and  
11 deep vein thrombosis.

12 The second are investigator reported thrombotic  
13 cardiovascular events. These represent the larger group of  
14 unadjudicated thrombotic events as reported by the  
15 investigators. So, in essence, these are unadjudicated  
16 events.

17 Lastly, is the APTC endpoint, which is the  
18 combined endpoint used by the anti-platelet trials  
19 collaboration. This is the most common and widely accepted  
20 endpoint used to quantify the overall cardiovascular impact  
21 of antithrombotic compounds in cardiovascular trials. This  
22 endpoint, which measures fatal and irreversible morbid  
23 cardiovascular events, is the combined incidence of  
24 cardiovascular and unknown cause of death, and it does  
25 include hemorrhagic deaths, myocardial infarctions and

1 cerebral vascular accidents. This is considered the gold  
2 standard endpoint for the analyses of thrombotic  
3 cardiovascular events.

4 [Slide]

5 I am going to start the review of cardiovascular  
6 safety with the VIGOR results which did demonstrate a  
7 significantly reduced incidence of thrombotic adverse events  
8 on naproxen compared to rofecoxib. However, to further  
9 understand the reason for the difference between these two  
10 treatment groups, we examined in detail the results from  
11 both our Phase IIb/III OA studies which compared rofecoxib  
12 to placebo and NSAIDs without sustained anti-platelet  
13 activity, as well as from two large, ongoing placebo-  
14 controlled studies in elderly patients with Alzheimer's and  
15 mild cognitive impairment. Lastly, we performed a formal  
16 meta-analysis of cardiovascular results from all of our  
17 Phase IIb through V rofecoxib clinical trials.

18 The totality of data from these analyses  
19 demonstrated that the risk of sustaining a cardiovascular  
20 event on rofecoxib is similar to placebo and to NSAIDs  
21 without sustained anti-platelet activity. The reduction in  
22 events on naproxen compared with rofecoxib appears to be the  
23 outlier.

24 [Slide]

25 In VIGOR there were 45 confirmed thrombotic events

1 on rofecoxib compared to 19 on naproxen. The relative risk  
2 of sustaining a thrombotic event on naproxen compared to  
3 rofecoxib was 0.42. The 95 percent confidence intervals you  
4 see here do not cross 1 and that implies statistical  
5 significance. Although there was a reduction in confirmed  
6 cardiovascular events, the cardiovascular mortality was low  
7 and similar in the two groups.

8           Now, if you break down the events by location,  
9 what you can see is that the majority of events were cardiac  
10 events and the majority of the reduction was in cardiac  
11 events. In the cardiac event category most of the events  
12 were myocardial infarctions and there was, in fact, a  
13 significant reduction in myocardial infarctions in the  
14 naproxen group compared to the rofecoxib group.

15           To better understand these results, we looked at  
16 the clinical characteristics of patients with events and we  
17 found that the patients who had thrombotic events were those  
18 who you would have expected to have thrombotic events. They  
19 were older than the overall cohort. Higher percentage of  
20 them were males, and close to 80 percent had one or more  
21 cardiovascular risk factors.

22           [Slide]

23           In addition, we explored any possible association  
24 between hypertension and cardiovascular events. NSAIDs and  
25 COX-2 inhibitors are both associated with small increases in

1 systolic blood pressure and, as I noted earlier, there was a  
2 higher incidence of hypertension adverse experiences on  
3 rofecoxib compared to naproxen. Therefore, although it  
4 wasn't unexpected that small increases in blood pressure in  
5 this one-year study could explain the imbalance in  
6 cardiovascular events, it was important that we investigated  
7 any potential interaction and none was found.

8           We looked at patients with confirmed  
9 cardiovascular events to determine how many were preceded by  
10 a hypertensive adverse experience. Of the 45 patients on  
11 rofecoxib who had a confirmed cardiovascular event, only  
12 four had an antecedent hypertensive adverse experience and,  
13 as you can see, one had a deep vein thrombosis, two had  
14 cerebral vascular accidents, one had a myocardial  
15 infarction. In addition, overall changes in blood pressure  
16 were similar in rofecoxib patients who had cardiovascular  
17 events compared with patients who did not have  
18 cardiovascular events.

19           [Slide]

20           So, in VIGOR there was a significantly decreased  
21 incidence of serious thrombotic cardiovascular events on  
22 naproxen compared to rofecoxib. However, when you review  
23 the results of VIGOR in isolation you don't know whether the  
24 imbalance of cardiovascular events was caused by a decrease  
25 in events on a platelet-inhibiting NSAID, naproxen, or an

1 increase in events on a COX-2 selective inhibitor due to  
2 inhibition of prostacyclin without concomitant anti-platelet  
3 effects.

4 [Slide]

5 The best way to differentiate between those two  
6 possibilities was to examine the cardiovascular results in  
7 the rest of the rofecoxib development program where  
8 rofecoxib was compared to other NSAIDs and, most  
9 importantly, to placebo.

10 [Slide]

11 In the combined Phase IIb/III OA studies, again,  
12 the treatment groups were rofecoxib, the combined NSAID  
13 group and placebo. Again, the combined NSAID group was  
14 diclofenac, ibuprofen and nabumetone, most of the experience  
15 being in diclofenac and ibuprofen. None of these maintained  
16 more than 90 percent inhibition of platelet aggregation  
17 throughout the entire dosing interval and, therefore, you  
18 would not expect them to be effective antithrombotic agents.

19 [Slide]

20 The incidence of investigator reported  
21 cardiovascular events is presented here as rates per 100  
22 patient years, with the number of events in parentheses next  
23 to these. The rate of events on rofecoxib, as you can see,  
24 in these studies was 2 versus 2.3 events per 100 patient  
25 years in the combined NSAID group, and in those studies

1 which had placebo the incidence of events was again similar,  
2 2.5 versus 2.4. As you can see, the overall incidence of  
3 events was relatively low.

4 I just want to point out that I switched to  
5 investigator reported cardiovascular events, and the reason  
6 that I had to do that is that the cardiovascular SOP was  
7 instituted after the completion of these studies. But what  
8 we saw in VIGOR was that the investigator reported events  
9 were very similar to confirmed events. Both had about a 50  
10 percent reduction on naproxen compared to rofecoxib.

11 [Slide]

12 On the vertical axis here is the cumulative  
13 incidence of investigator reported cardiovascular events,  
14 with time on the X axis. In blue is the NSAID comparison  
15 group from OA. In yellow is the rofecoxib group.

16 I am now going to overlay on that the results from  
17 the VIGOR study. In yellow, again, is rofecoxib from VIGOR  
18 and down here you see naproxen, and what you see is that the  
19 outlier here is naproxen, which is lower than any of the  
20 other treatment groups.

21 [Slide]

22 The results of the Phase IIb/III studies  
23 demonstrated that the risk of sustaining a cardiovascular  
24 event was similar on rofecoxib compared to NSAIDs without  
25 sustained anti-platelet effects, as well as to placebo but,

1 as I pointed out, the amount of placebo-controlled data in  
2 the OA database is relatively small and, therefore, the  
3 Alzheimer's studies were important because they provide  
4 extensive long-term placebo-controlled data in the elderly  
5 patient population. Thus, these studies provide very  
6 informative data on the safety profile of rofecoxib compared  
7 to placebo.

8 [Slide]

9 We did a combined analysis of two large studies.  
10 The patient populations in the studies are similar. Again,  
11 this is an interim analysis. The treatment groups in these  
12 studies are 25 mg of rofecoxib versus placebo. And, we say  
13 high risk in that this is an elderly patient population.  
14 The mean age of the patients was 75 years of age. The  
15 majority of the patients were male. Over 50 percent had one  
16 or more cardiovascular risk factors. As of September, 2000  
17 there were over 1000 patients and over 1200 patient years in  
18 each treatment group, with a median duration of therapy of  
19 12.5 months.

20 [Slide]

21 Again, I am reporting here investigator reported  
22 events; number of events over here; rates of events over  
23 here. For rofecoxib you can see 2.8, 3.3 on placebo. We  
24 just recently received the results of confirmed events that  
25 were recently reported by the adjudication committee and, in

1 fact, the results are quite similar with, again, a small  
2 numerical increase in events on placebo compared to  
3 rofecoxib but statistically similar.

4 [Slide]

5 The incidence of investigator reported  
6 cardiovascular events over time is illustrated on this  
7 slide. The visual impression is that there is an increase  
8 in event rate, especially at the end of the curve and  
9 especially in the placebo group. Something similar was seen  
10 in the VIGOR study in the rofecoxib treatment group. It is  
11 important to remember that as patient exposure diminishes as  
12 you go out here, the cumulative incidence estimates become  
13 much less precise. In all of these studies -- VIGOR and the  
14 Phase IIb/III studies, as well as in the Alzheimer's studies  
15 -- there was a constant relative risk over time. Again, I  
16 just want people to realize that white, here, is placebo;  
17 yellow, here, is rofecoxib.

18 [Slide]

19 As I noted earlier, the gold standard endpoint for  
20 assessing cardiovascular impact of antithrombotic agents is  
21 the combined APTC endpoint. This slide shows the relative  
22 risk, in diamonds, with 95 percent confidence intervals of  
23 sustaining an APTC endpoint on comparator versus rofecoxib.  
24 Triangles that fall to the left of 1 favor the comparator  
25 agent. Triangles which fall to the right favor rofecoxib.

1 The relative risk of sustaining an APTC endpoint, you can  
2 see in the Phase IIb/III studies where non-naproxen NSAIDs  
3 are compared to rofecoxib, is not statistically different  
4 between the two groups. Numerically, if anything, it  
5 favored rofecoxib and, again, in the Alzheimer's placebo-  
6 controlled studies there was no difference between the two  
7 groups. The outlier here is the naproxen data versus  
8 rofecoxib from the VIGOR study, which favored naproxen with  
9 a reduced incidence of events.

10 [Slide]

11 One way to put together the cardiovascular data  
12 across all of the studies is to do a meta-analysis. This  
13 meta-analysis included all of our Phase IIb through V  
14 studies which were completed by September, 2000 and were  
15 four weeks or more in duration. The exception here, again,  
16 is the Alzheimer's studies which are still ongoing, for  
17 which interim data was used. The APTC endpoint which, as I  
18 said, is the gold standard was chosen as the predefined  
19 endpoint for the meta-analysis.

20 [Slide]

21 This meta-analysis includes data on over 28,000  
22 patients and over 14,000 patient years. Therefore, it  
23 ensures both power and precision.

24 [Slide]

25 The results of the meta-analysis confirm the

1 cardiovascular results that I just showed you for VIGOR, the  
2 Phase IIb/III OA studies and the Alzheimer's studies.

3 Again, you see the comparisons to placebo and non-naproxen  
4 NSAIDs, and the outlier here is the comparison to naproxen.

5 Now, since this meta-analysis combines studies of  
6 varying duration and dose of rofecoxib, a series of  
7 sensitivity analyses were done at the request of the FDA to  
8 see if either of these variables impacted the overall  
9 results.

10 [Slide]

11 To ensure that studies of short duration did not  
12 unduly influence the results, the meta-analysis was repeated  
13 using studies of six months or more in duration, and the  
14 results look almost identical to those I just showed you.

15 [Slide]

16 In addition, we evaluated the effect of rofecoxib  
17 dose. This latter analysis was limited by small numbers of  
18 events, however, a dose relationship was not observed. To  
19 evaluate this you can only combine studies in which each of  
20 the treatments was evaluated, and there was only one small  
21 study which had all three treatment groups, 12.5, 25 and 50,  
22 and, therefore, we combined studies that had both 12.5 and  
23 25, over here, and 25 and 50 and, again, no apparent dose  
24 relationship was observed.

25 So, how can the cardiovascular results of

1 rofecoxib compared to naproxen in VIGOR be reconciled with  
2 the results compared to placebo or non-naproxen NSAIDs? In  
3 aggregate, the clinical pharmacology data and clinical study  
4 data shown in the last several slides are consistent, with  
5 the explanation that in VIGOR the imbalance in  
6 cardiovascular events was due to naproxen reducing the risk  
7 of sustaining an event rather than rofecoxib increasing the  
8 risk.

9 [Slide]

10 Given these results, we were interested in  
11 determining whether there was any in vivo evidence in VIGOR  
12 of naproxen's ability to inhibit platelet function.  
13 Aspirin's effects on platelet function lead to an increased  
14 risk of minor bleeding events, such as epistaxis and  
15 ecchymoses, as Dr. Nies just mentioned, and in VIGOR  
16 naproxen was associated with a two- to three-fold increase  
17 in both ecchymoses and epistaxis compared to rofecoxib.  
18 Thus, there was in vivo evidence of naproxen's effect on  
19 platelet function.

20 [Slide]

21 Before I summarize the data presented by both Dr.  
22 Nies and myself this morning, I want to take a moment to  
23 review with you the data which does support naproxen's  
24 ability to act as an anti-platelet agent. The results of  
25 recently completed animal studies which have not yet been

1 fully reviewed by the FDA, in an animal monkey model of  
2 acute thrombosis, have demonstrated that naproxen does have  
3 an antithrombotic effect which is similar to aspirin. We  
4 can show you the results of those later today.

5           As we have already shown you, the clinical  
6 pharmacology data shows that naproxen has sustained anti-  
7 platelet effects throughout its dosing interval, and these  
8 effects are different than those that are seen with  
9 ibuprofen. It also has aspirin-like increases in bleeding  
10 time. If you look at the naproxen label, which is actually  
11 different than either the ibuprofen or diclofenac label, it  
12 specifically states that naproxen increases bleeding time.  
13 Although there are no randomized clinical studies which have  
14 evaluated naproxen's ability to act as a cardioprotective  
15 agent, there is evidence from randomized clinical controls  
16 of other reversible, non-selective inhibitors which are  
17 potent anti-platelet agents, and these include studies with  
18 indobufen which is approved in countries outside of United  
19 States as a cardioprotective agent, not as an anti-  
20 inflammatory agent, and this agent has been shown to  
21 decrease graft occlusion and decrease thromboembolic events.  
22 In addition, flurbiprofen has been shown in one study to  
23 decrease the rate of recurrent MI by 70 percent compared to  
24 placebo.

25           Secondly, if you look at the incidence of

1 cardiovascular events or myocardial infarctions across all  
2 of our treatment arms and all of our other databases, the  
3 rates are similar. Lastly, as I just showed you, there was  
4 an increased incidence with aspirin-like bleeding adverse  
5 experiences in VIGOR, which goes along with the anti-  
6 platelet activity that we think naproxen has.

7           We have also recently completed an epidemiologic  
8 study in the Great Britain general practice database. The  
9 results of this have only recently been shared with the  
10 agency since we just received approval from the external  
11 review board of that database to share these results  
12 publicly. But, this study did demonstrate a significant  
13 reduction in the risk of sustaining a thrombotic event in  
14 patients with rheumatoid arthritis who were treated with  
15 naproxen. Thus, there is substantial data which supports  
16 naproxen's ability to act as a cardioprotective agent.

17           [Slide]

18           In summary, rofecoxib is a COX-2 inhibitor without  
19 effects on COX-1 at and above the clinical doses. It  
20 demonstrates analgesic and analgesic and anti-inflammatory  
21 efficacy similar to non-selective NSAIDs in OA in acute  
22 pain, but it is associated with significantly fewer  
23 clinically important GI events compared with non-selective  
24 NSAIDs. This has been demonstrated independently in OA and  
25 in RA. We have seen consistent significant reductions in

1 all endpoints, consistent significant reductions in high and  
2 low risk subgroups, and all of these results have shown  
3 that, in fact, endoscopic studies do translate into clinical  
4 GI outcomes.

5 [Slide]

6 Rofecoxib is generally well tolerated. The renal  
7 effects of rofecoxib and COX-2 inhibitors are similar to  
8 non-selective NSAIDs, are consistent with our currently  
9 approved labeling. Discontinuations are rare, and  
10 differences that were seen in VIGOR between 50 mg rofecoxib  
11 dose and 1000 mg naproxen dose, in mechanism-based, dose-  
12 dependent adverse events are consistent with the dose  
13 disparity. Lastly, there was a low incidence of  
14 transaminase elevations associated with rofecoxib.

15 [Slide]

16 In terms of cardiovascular safety, the risk of  
17 cardiovascular events on rofecoxib are similar to placebo  
18 and NSAIDs without sustained and nearly complete inhibition  
19 of platelet function, and the decreased cardiovascular  
20 events with naproxen in VIGOR is consistent with its potent  
21 anti-platelet effects. All of these cardiovascular results  
22 are consistent with rofecoxib's COX-2 selective and,  
23 therefore, its lack of anti-platelet activity.

24 [Slide]

25 This development program has clearly demonstrated

1 that the COX-2 selective inhibitor rofecoxib has efficacy  
2 similar to NSAIDs but with a significantly improved GI  
3 safety profile. Its effects on renal sodium handling are  
4 similar to NSAIDs and the risk for sustaining a thrombotic  
5 event is similar to placebo.

6 The COX-2 hypothesis has been confirmed, and we  
7 believe that these data warrant modification to the current  
8 rofecoxib label to distinguish the GI safety profile of  
9 rofecoxib compared to non-selective NSAIDs. Thank you.

10 DR. HARRIS: I am going to ask the committee,  
11 because that was a lot of data that was presented, whether  
12 or not there are any questions to clarify -- any questions  
13 of clarity? There are several hands. I am going to start  
14 on my right today. Dr. Elashoff?

15 DR. ELASHOFF: Yes, I have questions about four  
16 slides. The first is 96, and what I wanted is standard  
17 errors, standard deviations, confidence intervals, any kind  
18 of indication of variability in those and in the comparison  
19 between them.

20 DR. REICIN: There were no substantial differences  
21 in those. You can see they were virtually identical, and I  
22 do not have a slide with standard errors but we can provide  
23 those to you.

24 DR. ELASHOFF: Okay. The next is slide 115, where  
25 there is a statement made about changes from baseline blood

1 pressure that were similar, and I would like to see standard  
2 errors or confidence intervals for that statement.

3 DR. REICIN: We did a variety of analyses and,  
4 again, you know, you are talking about few events and so I  
5 am sure the standard errors are large. I don't have a slide  
6 with that. We looked both at changes from baseline and we  
7 also looked at patients who had predefined limits of change.

8 DR. ELASHOFF: Because means might appear to be  
9 similar but you have a huge confidence interval so that you  
10 can't make much of it.

11 Slide 120, I would like to see a version of that  
12 slide with the different NSAIDs broken down and the  
13 different doses of rofecoxib broken down.

14 DR. REICIN: There were too few events to break  
15 that out like that. We do not have a survival analysis done  
16 in that way.

17 DR. ELASHOFF: And, slide 127, I didn't pick up  
18 the distinction between thrombotic cardiovascular events and  
19 APTC events.

20 DR. REICIN: Sure, the major distinction between  
21 those is that thrombotic events include transient ischemic  
22 attacks, unstable angina, deep vein thrombosis, arterial  
23 thrombosis. Those are not included in the APTC endpoint.  
24 In addition, the APTC endpoint includes unknown cause of  
25 death, which is not included in the thrombotic endpoint, and

1 it also includes hemorrhagic death.

2 DR. ELASHOFF: Thank you.

3 DR. HARRIS: Dr. Harell, I will give you a chance  
4 since we are moving right to left.

5 DR. HARRELL: I have two issues. One is on slide  
6 89. In looking at the CV safety you were pretty quick to  
7 bring in other comparators and breakouts. I would like to  
8 see a breakout of the comparators on this slide.

9 DR. REICIN: Dr. Simon, do you want to come up?

10 DR. SIMON: Sure. Tom Simon, GI research at  
11 Merck.

12 [Slide]

13 What this slide represents is a combined analysis  
14 of the Phase IIb/III studies looking at GI endpoints. The  
15 trial was prospectively defined to compare NSAIDs as a group  
16 against rofecoxib, all doses combined as a group, and that  
17 is because all of those studies had at least one dose of  
18 rofecoxib and one of the NSAIDs. So, that is how the study  
19 was constructed and those are the main results.

20 One of the problems you have when you breakout the  
21 NSAIDs individually is that there is confounding by protocol  
22 type. Not every type of protocol -- there were endoscopy  
23 studies, short-term studies and long-term studies and not  
24 every NSAID is represented in every type of protocol. So,  
25 when you look at them separately there is this caveat around

1 it.

2 [Slide]

3 Just to show you the data since you asked, I would  
4 like to start with the diclofenac results. What we have  
5 done here is to break diclofenac out of the studies, and you  
6 can see that numerically there is a trend in favor of  
7 rofecoxib. The point estimate for the relative risk  
8 reduction is 0.86, however, the confidence interval is broad  
9 because the number of patient years is small. That is true  
10 when you look at the confirmed PUB events, which is the  
11 primary endpoint, and also true when you look at the  
12 secondary endpoint.

13 DR. ELASHOFF: Dose of rofecoxib?

14 DR. SIMON: That is all doses combined. Looking  
15 at the confirmed plus unconfirmed events, there is again the  
16 same trend.

17 [Slide]

18 This is looking at ibuprofen and you can see that  
19 the difference between rofecoxib doses combined and  
20 ibuprofen is larger. That relative risk is shown here,  
21 again, less than 1 in favor of rofecoxib and the confidence  
22 intervals are also illustrated.

23 [Slide]

24 Lastly, I would like to show you slide 80. What  
25 this illustrates is some of the consistency of the results

1 favoring rofecoxib. This is the result with all protocols  
2 combined, looking at rofecoxib doses combined versus NSAIDs.  
3 What has been done here is that each of the individual  
4 protocol types has been removed serially to show you what  
5 the results look like when you take out the different types  
6 of protocol. This is protocol 029. This is an ibuprofen  
7 study. When you take it out the result is consistent. This  
8 is also with ibuprofen taken out and the result is  
9 consistent. This is a diclofenac study. These are the OA  
10 efficacy studies. When you take those out the results are  
11 also consistent favoring rofecoxib. Finally, when you take  
12 out the endoscopy studies you get a point estimate that  
13 favors rofecoxib as well. This last study is a nabumetone  
14 trial again and if you take that out the results are still  
15 consistent.

16 DR. HARRELL: Thank you. My second question is at  
17 some point during the VIGOR study, presumably the DSMB saw a  
18 significant difference in serious CV event rates, yet they  
19 didn't stop the study. What were the operating procedures  
20 that were in effect, or what documentation did the DSMB have  
21 regarding this point?

22 DR. REICIN: I think I am going to have Dr. Neaton  
23 answer that question. Dr. Neaton was a member of the DSMB  
24 and since I was not privy to those meetings I think it is  
25 most appropriate for him to answer those questions.

1 DR. NEATON: Maybe I can try to answer it and then  
2 you can be more specific with your question. We reviewed  
3 the data analysis plan in advance of reviewing the data and  
4 approved that, and we met three times during the fall of  
5 1999. The first analysis was preplanned to look at the GI  
6 toxicities. The criteria were both for PUBs and complicated  
7 PUBs. The PUB criteria were met, the complicated was not.  
8 It was close. Because during the discussions of the data  
9 analysis plan, of the design of the study, a great deal of  
10 emphasis was placed on the complicated and even though it  
11 was close we decided to continue. We noticed at that point  
12 a trend for the cardiovascular events and requested  
13 additional analyses, and those were reviewed on two  
14 different occasions, later, I believe, in November and again  
15 in December. The additional analyses requested were  
16 primarily to take advantage, to the extent we could, of the  
17 different sources of data that were being presented to us on  
18 discontinuations, on adverse events coming from different  
19 databases.

20 You are correct, there was a nominally significant  
21 difference in cardiovascular events, I believe, even on the  
22 second occasion when we reviewed it, but these were  
23 unadjudicated events and we were combining the events in a  
24 way that we felt was relevant. We felt ultimately that it  
25 was probably in terms of continuing this trial to get more

1 definitive data on precisely the nature of the  
2 cardiovascular events and the differences between the two  
3 treatment groups to balance that against what we were seeing  
4 or, rather substantial efficacy or reduction in the GI  
5 toxicities. So, at our last meeting, which was close to the  
6 time when the trial was scheduled to end, we requested that  
7 the events for VIGOR be adjudicated. There was an  
8 adjudication protocol that we were made aware of in the pre-  
9 study planning and design. But, we were not clear that the  
10 timetable for the adjudication of those events was in sync  
11 with the completion of the VIGOR study. So, we felt that to  
12 properly balance kind of the positive and negative sides of  
13 treatment A versus treatment B, we felt that those should be  
14 adjudicated before the results were unblinded. So, we made  
15 that request at our last meeting.

16 But, the DSMB was provided information by the  
17 study statistician, Dr. Shapiro. We reviewed that  
18 information. They were very responsive to every request we  
19 made for additional data. From that point of view, the  
20 information we received was outstanding and the  
21 responsiveness was outstanding.

22 DR. HARRELL: Was the DSMB blinded throughout this  
23 process?

24 DR. NEATON: The DSMB was blinded. We chose up  
25 front that the treatments would be coded A and B. However,

1 after the first look, as in most cases, we anticipated  
2 probably what the results were. So, we never really  
3 requested to be unblinded but I think it is probably fair to  
4 say that we had a notion of which way the results were  
5 going.

6 DR. HARRELL: And, did the DSMB have any written  
7 minutes about reasons for not terminating the study?

8 DR. NEATON: For not terminating the study -- I  
9 think probably there were a variety of reasons in all of our  
10 minds. One of them had to do with something I mentioned  
11 earlier about specifically how to combine the serious  
12 cardiovascular events. They were broken down individually  
13 and we basically chose to combine them in groups that we  
14 thought were relevant, as well as kind of to try to merge  
15 what were recorded as adverse events and reasons for  
16 discontinuation. There was a small excess of deaths on  
17 treatment A that was not significant. The most serious  
18 event that you might consider was a little worrisome but was  
19 not so pronounced -- and the numbers were very small. More  
20 generally, for the major cardiovascular events, the numbers  
21 were small and were unadjudicated.

22 So, I think that there was speculation on the part  
23 of some people on the board that this could be a protective  
24 effect of naproxen, treatment B as we referred to it at the  
25 time. I don't think that was the reason for our allowing it

1 to continue. At least personally, and I think other people  
2 shared this, it was to get more definitive information on  
3 this because we felt it would be an important thing to have  
4 good data both on these cardiovascular events and GI events,  
5 and while we have superb adjudicated data on GI events, the  
6 data on the cardiovascular events were coming from different  
7 databases and we felt that they should be kind of collected  
8 and presented ultimately in the same quality as the GI  
9 events.

10 DR. HARRELL: Thank you.

11 DR. REICIN: Dr. Elashoff, on page 27 of the  
12 background package, Table 6 for the efficacy measurements,  
13 you can see standard deviations and 95 percent confidence  
14 intervals. Standard errors are not on that table but for  
15 all three efficacy endpoints the standard errors were 0.015.

16 DR. ELASHOFF: Pardon me, I wasn't listening quick  
17 enough. It is Table 6, which I just found --

18 DR. REICIN: Right, the standard errors are not  
19 provided in that table. It is standard deviations in that  
20 table. The standard errors were 0.015.

21 DR. ELASHOFF: Thank you.

22 DR. SAMPSON: Allan Sampson. I wanted to follow-  
23 up on Dr. Harrell's question about slide 89. Maybe it is in  
24 the background document, but do you have that for the  
25 complicated upper GI events, the so-called POBs? That is

1 for POBs, right?

2 DR. REICIN: This is for POBs. I think there were  
3 only nine complicated events in the study.

4 DR. SIMON: I don't have that broken out by dose  
5 but the problem is there is only a small number of PUBs.

6 [Slide]

7 What you are looking at here is the incidence of  
8 perforations, obstructions and bleeds that occur over time.  
9 I actually don't know which NSAIDs those are on but we felt  
10 that the numbers were so small that we didn't break them out  
11 separately.

12 DR. SAMPSON: Second question, there was slide 41  
13 on platelet aggregation, naproxen versus ibuprofen, and that  
14 was truncated at 8 hours. Since one is a t.i.d. dosing and  
15 one is b.i.d. dosing, would you have that going out to 12  
16 hours?

17 DR. NIES: Yes, as I explained when I began, this  
18 is at steady state. This is after 5 days of dosing. The  
19 first point is 12 hours after the previous dose. So, that  
20 is the 12-hour time point for naproxen. It is the 8-hour  
21 time point for ibuprofen. We do have another 8-hour time  
22 point at the end of the dosing interval for ibuprofen. For  
23 naproxen we didn't go out another 12 hours. But we assumed,  
24 since the 12 hours from the previous dose was already  
25 completely inhibited, it would stay that way.

1 DR. SAMPSON: I understand. Thank you. I have  
2 one other question. There was something we say yesterday  
3 that was an interesting summary, and that was the incidence  
4 of significant hematocrit and hemoglobin drops, and I think  
5 it was defined by hematocrit less than 10 percent and  
6 hemoglobin less than 2 gm. Do you have a comparison on that  
7 that you could show us?

8 DR. REICIN: Yes, we do.

9 [Slide]

10 As you see, there was a numeric trend. It did not  
11 reach statistical significance for rofecoxib compared to  
12 naproxen. I think part of this is that you have fluid  
13 retention also having an impact here. As Dr. Nies  
14 mentioned, we have studies which have actually looked at  
15 clinical GI blood loss, giving patients tagged red blood  
16 cells, and that has shown a significant reduction in  
17 subclinical GI blood loss. In fact, in our Phase IIb/III OA  
18 studies, at the 25 mg dose we did see a significant  
19 reduction in those type of hemoglobin/hematocrit changes but  
20 at the 50 mg dose, because of fluid retention, the  
21 differences are diminished.

22 You can see here a decrease in hemoglobin of more  
23 than 2 g/dL and hematocrit of more than 5 percent, or  
24 hemoglobin or more than 1 drop, or a hematocrit drop of more  
25 than 10 percent, there at the bottom. You can see numeric

1 trends but this did not reach statistical significance.

2 DR. SAMPSON: Thank you. One final, more  
3 technical question for my own clarification, VIGOR was run  
4 under two separate protocol, 88 and 89 --

5 DR. REICIN: That was an administrative issue  
6 because one protocol was outside the U.S. and one was in the  
7 U.S. The started at exactly the same time. The protocols  
8 were identical. Everything was handled -- there was one  
9 database. The endpoints came in, in the same way. It was  
10 merely administrative.

11 DR. SAMPSON: But, as I understand it, one was  
12 restricted to sites in the U.S. and one was sites  
13 internationally.

14 DR. REICIN: Correct, and because of the way we  
15 conduct studies outside the U.S. it had to be under a  
16 separate protocol number.

17 DR. SAMPSON: Were there analyses done -- I have  
18 no access to these -- that looked at the protocols  
19 separately, looking both at potential effects or differences  
20 due to sites in the U.S. versus ex-U.S.?

21 DR. REICIN: We did both our GI analysis and our  
22 cardiovascular analysis that way, and we had basically  
23 similar results both in the U.S. and outside the U.S.

24 DR. SAMPSON: Thank you.

25 DR. HARRIS: Dr. Wofsy?

1 DR. WOFSY: Thank you, my question has been asked  
2 and answered.

3 DR. HARRIS: We will go around the table. Yes?

4 DR. PINA: I need several clarification points  
5 about your comparison group of I Ib and III. Were group II  
6 healthy volunteers?

7 DR. REICIN: I Ib, no. The I Ib are dose-ranging  
8 studies in osteoarthritis. So, the I Ib/III studies are all  
9 osteoarthritis patients. All those protocols had very  
10 similar inclusion and exclusion criteria.

11 DR. PINA: Do you have a comparison of the patient  
12 population demographics --

13 DR. REICIN: I do.

14 DR. PINA: -- between those and VIGOR?

15 DR. REICIN: Yes, I do.

16 DR. PINA: I would be interested to see if the  
17 populations are different.

18 You will see they were not exactly the same but  
19 similar, as we are looking for the slide. The mean age in  
20 VIGOR was about 58. The mean age in the Phase I Ib/III OA  
21 studies was 62.

22 [Slide]

23 There were, I think, about 7 percent more males.  
24 You can see the Phase I Ib/III results over here, on the left  
25 and VIGOR on the right. You can see the percent of patients

1 with any cardiovascular risk factor is similar, not exactly  
2 identical, and past history of atherosclerotic disease is  
3 similar, not identical.

4 DR. PINA: Was the decision to enter patients  
5 based on their need for concomitant aspirin left up to the  
6 individual investigator in VIGOR?

7 DR. REICIN: Yes, it was. We specifically in the  
8 protocol told people not to take patients off aspirin in  
9 order to allow them to enter the study.

10 DR. PINA: And, what was your definition of  
11 hypertension?

12 DR. REICIN: That is left up to the investigators.  
13 So, it is reported on the past medical history form, and  
14 adverse experiences during the study are, again, reported by  
15 the investigators.

16 DR. PINA: But was there a definition for this  
17 event since you were capturing hypertension?

18 DR. REICIN: There was no definition for it.

19 DR. PINA: Then, one last question, of the  
20 patients who had ecchymoses as you are using ecchymoses as a  
21 sign of platelet dysfunction, how many of those patients  
22 were on steroids?

23 DR. REICIN: We didn't do that analysis.

24 DR. PINA: You had a certain number of patients on  
25 steroids --

1 DR. REICIN: Over 50 percent of patients were on  
2 steroids. It is actually an interesting question.

3 DR. WOLFE: I have a few questions.

4 DR. HARRIS: Can you just say your name into the  
5 microphone?

6 DR. WOLFE: I am sorry, Michael Wolfe. I have a  
7 few questions. One comes back to the question of the IIb  
8 and III OA patients. Were they allowed to take a low dose  
9 of aspirin?

10 DR. REICIN: No, low dose aspirin was also not  
11 allowed in those studies, except for one very small study in  
12 the elderly that maybe makes up 100 of the patients.

13 DR. WOLFE: Speaking of small numbers, you showed  
14 some of the data comparing rofecoxib with diclofenac and  
15 ibuprofen, but do you have any comparison -- again, I am  
16 sure the numbers are very small -- of rofecoxib versus  
17 nabumetone?

18 DR. REICIN: Yes, we do, and you are asking  
19 specifically about --

20 DR. WOLFE: The number of POBs or PUBs.

21 DR. REICIN: In our nabumetone studies there were  
22 no endpoints in any of the groups.

23 DR. WOLFE: Too small.

24 DR. REICIN: Yes. That is why I tried to be very  
25 clear in my talk to say that really most of the experience

1 was on diclofenac in that regard.

2 DR. WOLFE: I have another question regarding the  
3 H-2 blockers in VIGOR. I realize there is only over-the  
4 counter dosing but you mentioned dose creep, and there is  
5 certainly dose creep with H-2 blockers over-the-counter and  
6 one of your consultants has data suggesting that high dose  
7 of famotidine may be protective. Do you have any  
8 information on the amount of H-2 blockers used?

9 DR. REICIN: Yes, I do.

10 [Slide]

11 Slide 184 shows the use of GI co-medication --  
12 this is any, so if you took one dose you count here --  
13 during the study and, not surprisingly, H-2 blockers are  
14 used more than any of the others because they were allowed,  
15 and very low use of proton pump inhibitors.

16 DR. WOLFE: But do you have the amount? Did any  
17 of the patients take huge amounts of H-2 blockers? One dose  
18 is absolutely nothing. I personally think high doses don't  
19 do very much --

20 DR. REICIN: While I can't give you exact amounts,  
21 the majority of patients were on over-the-counter doses.  
22 There were a few that were taking higher doses, although we  
23 didn't look for super-therapeutic doses.

24 DR. SIMON: Tom Simon again just to make one  
25 point. If you want to prevent ulcers with an H-2 antagonist

1 like famotidine, you have to go to, like, 80 mg a day for a  
2 sustained period of time. So, that probably wouldn't be  
3 consistent with the type of OTC H-2 use as permitted in  
4 VIGOR.

5 DR. WOLFE: You would think that but I am sure  
6 there are people out there who figure if two are good, three  
7 and four are probably even better.

8 DR. HARRIS: Dr. Cryer?

9 DR. CRYER: This continues along the line of  
10 questions comparing your Phase IIb/III and VIGOR results.  
11 You suggest that the GI event rate in your RA population was  
12 generalizable to a larger population because the relative  
13 risk reduction in your clinical GI events in VIGOR and your  
14 RA patients were similar to the IIb/III OA studies.  
15 However, as has been pointed out, the OA studies had an  
16 average dose of rofecoxib that was about 25 mg. The  
17 question is do you have an analysis of the event rate in  
18 your OA studies using just the 50 mg dose of rofecoxib?

19 DR. REICIN: Dr. Simon?

20 DR. SIMON: Actually, we have stayed away from  
21 that for the reasons that I mentioned earlier about not  
22 wanting to split the doses out separately. There isn't  
23 enough exposure in each of the doses to look at them  
24 consistently. The other problem you run into actually when  
25 you try to break up the dose-response curve, it ends up

1 looking U-shaped and the placebo ends up being between the  
2 lowest rofecoxib dose and the highest rofecoxib dose, and  
3 that is part of why we think that method of analysis is just  
4 not a reliable way to look at the data.

5 [Slide]

6 I have indicated it is a little bit complicated  
7 but let me just take you through this. Here is what is  
8 happening, we have indicated that this analysis combined  
9 protocols of several different types. This is a Phase  
10 IIb/III dose-ranging study in OA. These are Phase III  
11 studies in OA. This is an endoscopy study and this is the  
12 elderly study.

13 The easiest thing to do probably is to look at the  
14 rate per 100 patient year columns. What you have to do if  
15 you mentally want to see what is going on with 50 is look at  
16 this column and this, and those look sort of high except  
17 that if you take a look at the 12.5 and then the placebo  
18 there is just an anomaly going on here. I think when you  
19 actually break the data out the numbers just start to get  
20 sparse when you try to stay consistent. That is the reason  
21 we have been leaning away from talking about 50 mg and how  
22 it compares to the other doses because the only data we have  
23 is just too sparsely populated when you look protocol type  
24 to accurately represent it.

25 DR. CRYER: I failed to introduce myself earlier,

1 Byron Cryer. I only have one other question. Did you  
2 detect any OTC NSAID use in your VIGOR trial?

3 DR. REICIN: There was very low usage of over-the-  
4 counter NSAIDs.

5 DR. CRYER: And, did that affect the outcomes in  
6 any way?

7 DR. REICIN: No. In fact, as a part of our per-  
8 protocol analysis, patients who used NSAIDs for more than 14  
9 days during the study were excluded from the per-protocol  
10 analysis, and for the per-protocol analysis the results were  
11 even stronger than the intention-to-treat analysis.

12 DR. HARRIS: Yes, Dr. Sampson?

13 DR. SAMPSON: One other question in trying to sort  
14 through the meta-analysis in the APTC. Do you have a  
15 breakdown, first of all, in RA patients excluding the VIGOR  
16 trial? Because what I would be interested in seeing is are  
17 there enough patients in RA taking naproxen that you can do  
18 another analysis that would give us a flavor, separate from  
19 VIGOR, of what it looked like in the other studies --

20 DR. REICIN: Yes. I will caveat by telling you  
21 that our entire Phase III program was done with naproxen as  
22 the comparison, and the RA results are mainly in VIGOR, but  
23 we did do an analysis in RA just specifically looking at the  
24 APTC endpoint. I am going to show that to you.

25 [Slide]

1           If you go to slide 289, this shows you the  
2 incidence of APTC events in our Phase IIb/III RA studies.  
3 The number of events is in parentheses, rates per 100  
4 patient years, and I think the numbers speak for themselves.  
5 I mean, only two events on 12.5.

6           Were you interested in seeing the epidemiologic  
7 data that we have in patients with rheumatoid arthritis?  
8 Can I turn that over to Dr. Guess to show you that data?

9           DR. SAMPSON: Sure.

10          DR. GUESS: These are some data from an analysis  
11 that we did in the U.K. general practice research database.

12          [Slide]

13          This is a large database in the United Kingdom  
14 that encompasses about 1500 general practitioners and about  
15 3 million people, about 5 percent of the population of the  
16 U.K. It is a database that is owned by the Medicines  
17 Control agency and they license it out. We conducted a  
18 study, completed it and just got the approval of the  
19 scientific review committee about two days ago to share the  
20 preliminary results with you, and I will go through the  
21 analyses that we looked at.

22          [Slide]

23          The objective of the study was to determine  
24 whether current use of naproxen is associated with a lower  
25 risk of acute major thrombotic events among rheumatoid

1 arthritis patients in the same age range we are looking at.

2 [Slide]

3 It was a case-control study among all of the  
4 17,000 eligible RA patients in GPRD. There were  
5 approximately 38,000 total patients when you exclude the  
6 ones that are not in the age range, and when you look at the  
7 exclusions that we have here, it comes down to 17,000  
8 patients, all of the patients with rheumatoid arthritis in  
9 the database. We excluded prior cardiovascular disease,  
10 cancer, vasculitis, coagulopathy, renal disease, liver  
11 failure, alcohol or drug abuse, aspirin, anticoagulants, and  
12 anti-platelet drugs. Controls, about 2000 of them, were  
13 matched to 720 cases on age, gender and medical practice,  
14 and there was adjustment for smoking, DMARDs, steroids,  
15 estrogen, diabetes, cardiovascular risk factors and other  
16 medical co-morbidities.

17 [Slide]

18 We took as a composite of acute myocardial  
19 infarction, sudden death and CVA, and it was like the APTC  
20 endpoint but it did not include hemorrhagic deaths or other  
21 forms of death. It was largely driven by the MI and the  
22 CVA. Only the first endpoint is looked at in a given  
23 analysis on a patient.

24 [Slide]

25 The exposure we had was current use of naproxen,

1 as defined by a prescription for naproxen within the past 30  
2 days prior to the index date, and the unexposed group were  
3 people that had not used naproxen within 365 days of the  
4 index date.

5 [Slide]

6 The preliminary results that we have here are that  
7 a current prescription for naproxen was associated with  
8 lower odds in an acute thromboembolic event than was known  
9 naproxen during the past year. The odds ratio was around  
10 0.6 with a confidence interval that didn't include 1, and  
11 adjustment for confounders didn't really change the results.

12 So, in this epidemiologic database we saw for the  
13 first time that current use of naproxen does appear to be,  
14 in RA patients, associated with a decreased risk of  
15 thromboembolic events in a very preliminary analysis.

16 DR. SAMPSON: Thank you. I was just wondering if  
17 it would be possible to get the preceding slide that Dr.  
18 Reicin showed, just a hard copy of that at some point by  
19 lunch time.

20 DR. REICIN: Yes, sure.

21 DR. HARRIS: Just to ask if that is doable.

22 DR. REICIN: Yes, absolutely.

23 DR. HARRIS: Dr. Nissen?

24 DR. NISSEN: Could you provide the actual event  
25 rates from that U.K. data, not just the odds ratios?

1 DR. GUESS: It is a case-control study so there  
2 would not be incident rates. In other words, in a case-  
3 control study you select people that have cases with the  
4 event and then you pick controls and you see which of those  
5 fractions had exposure to the drug. So, you wouldn't be  
6 able to get incidence out of that event.

7 DR. NISSEN: There just isn't any data available?

8 DR. GUESS: Well, you could analyze this as a  
9 cohort study but one of the problems with analyzing this as  
10 a cohort study with three million records is that we had a  
11 very limited period of time to do that. We actually have  
12 that on our plate to do but the data set is enormous and we  
13 did not have time to complete that type of analysis. It is  
14 on the plate to do.

15 DR. HARRIS: Since this may be a cardiovascular  
16 related question, I am going to ask Dr. Pina to ask the  
17 question.

18 DR. PINA: Your studies 085 and 090, are they  
19 included in that IIb/III OA composite analysis?

20 DR. REICIN: They were not included in the IIb/III  
21 OA composite analysis. They are, however, included in the  
22 meta-analysis that I showed you with non-naproxen NSAIDs.

23 DR. PINA: You allowed aspirin in those two  
24 trials?

25 DR. REICIN: We did allow aspirin in those two

1 trials.

2 DR. PINA: And in 090 there was a greater rate of  
3 thrombotic deaths in the rofecoxib group --

4 DR. REICIN: No deaths.

5 DR. PINA: No deaths?

6 DR. REICIN: Right.

7 DR. PINA: But thrombotic events?

8 DR. REICIN: Yes.

9 DR. PINA: Do you have that data?

10 DR. REICIN: What I can show you is the combined  
11 analysis we did from all of our aspirin users, looking in  
12 all of our studies that allowed aspirin. Can you go to  
13 slide 1639?

14 [Slide]

15 We had the two nabumetone studies that allowed  
16 aspirin. There was a small elderly study that allowed  
17 aspirin, a large advantage study that was a short-term study  
18 that also allowed aspirin, and also our Alzheimer's studies  
19 were amended recently to allow aspirin. So, this is an  
20 analysis we did looking at APTC endpoints in those that  
21 allowed concomitant aspirin.

22 What you can see is that the incidence of the APTC  
23 endpoints is almost identical in the two treatment groups,  
24 and then you look beneath it, patients who were not just in  
25 those studies taking concomitant aspirin.

1 DR. PINA: And then one last clarification, in  
2 your VIGOR trial toward the 8-month follow-up there seemed  
3 to be an acceleration of thrombotic events on your drug  
4 versus the naproxen. Do you have any explanation or any  
5 clarification about that?

6 DR. REICIN: As I mentioned when I showed you the  
7 placebo data with Alzheimer's, you saw almost that same type  
8 of acceleration out at the end of the curve there as well.  
9 Part of it is the visual impression of what you do with  
10 Kaplan-Meier curves. You have less people that have  
11 exposure as you go out, therefore, the estimates of the  
12 relative risk are much less precise out there.  
13 Statistically speaking though, we looked for constant  
14 relative risk over time and there was a constant relative  
15 risk over time.

16 DR. WOLFE: I have a cardiovascular question on  
17 VIGOR. If you exclude the people with a previous history of  
18 MI and/or high risk people in the analysis of thrombotic  
19 events do you see as big a difference between rofecoxib and  
20 naproxen?

21 DR. REICIN: You don't see as big a difference but  
22 you do still see a difference, and depending on the endpoint  
23 it sometimes reaches statistical significance and sometimes  
24 it doesn't. For MIs in particular it didn't, but the  
25 numerical trend is still there.

1 DR. HARRELL: A follow-up to that question, did  
2 you look at the traditional risk factor equations, like  
3 Framingham, and see if the risk factors operate the say way  
4 there?

5 DR. REICIN: You have to expand a little bit.

6 DR. HARRELL: So, if you put in your  
7 cardiovascular risk factors and age, and got the Framingham  
8 predicted risks and asked whether the Framingham risks  
9 predict the same way as they did in the Framingham  
10 population, or do risk factors in your study come in to have  
11 a different weight?

12 DR. REICIN: If I am understanding the question,  
13 all of the risk factors that you would expect to have higher  
14 event rates had higher event rates. So, older patients had  
15 higher event rates; males had higher event rates versus  
16 female patients with a history of hypocholesterolemia,  
17 higher event rates compared to those who did not. In each  
18 of those groups the relative risks were maintained. As I  
19 said, if you looked at the cohort of patients who had a  
20 confirmed event and you compared it to the entire VIGOR  
21 cohort, they were a higher risk patient population.

22 DR. HARRELL: And one step further, do the weights  
23 of the risk factors appear to be the same as risk equations  
24 that have been published in the literature?

25 DR. REICIN: We didn't do the analysis in that

1 exact way.

2 DR. HARRIS: Dr. DeLap?

3 DR. DELAP: I just wanted to add one cautionary  
4 note about the epidemiology U.K. data that you saw just a  
5 couple of minutes ago. That is new data to us as well as to  
6 the committee, and we have not completed review of it. So,  
7 we are not confident at this time to say what we will or  
8 will not be able to conclude once we do complete our reviews  
9 of those data.

10 DR. REICIN: I did mention that in my talk.

11 DR. HARRIS: Thank you. Does that conclude your  
12 presentation?

13 DR. REICIN: It concludes my presentation.

14 DR. HARRIS: Thank you very much. We are running  
15 about half an hour over, however, I am sure we need a 15-  
16 minute break, which we will have. We will convene again at  
17 10:45.

18 [Brief recess]

19 DR. HARRIS: I am calling the session back to  
20 order. We are now going to proceed with the FDA  
21 presentation, and we will start with Dr. Villalba providing  
22 a medical overview.

23 **FDA Presentation**

24 **Medical Overview**

25 DR. VILLALBA: Good afternoon, ladies and

1 gentlemen, members of the advisory committee. My name is  
2 Lourdes Villalba, and I am a medical officer in the Division  
3 of Anti-Inflammatory, Analgesic and Ophthalmic Drug  
4 Products.

5 [Slide]

6 We are here to talk about Vioxx Gastrointestinal  
7 Outcome Research, the VIGOR study. I won't be repeating  
8 many of the discussions that we had yesterday. Dr. Witter  
9 already gave you a background introduction and chronology of  
10 events related to the development of these protocols, and  
11 the sponsor has already presented in detail the VIGOR study.  
12 In this introduction, I just want to point out some issues  
13 that will be relevant for the afternoon discussion.

14 [Slide]

15 The VIGOR study was a large, randomized study with  
16 a follow-up of about nine months, and it was conducted to  
17 gather further information to characterize the GI safety  
18 profile of rofecoxib. Vioxx currently carries the GI  
19 warning label of the NSAID class and, based on this study,  
20 the sponsor proposes to downgrade the label and place a  
21 modified version under the precaution section of the label.

22 [Slide]

23 Now I would like to go straight to the issues that  
24 I want to discuss. First of all, treatment. The dose of  
25 rofecoxib used in the study was 50 mg a day. This is twice

1 the upper dose labeled for chronic use in osteoarthritis,  
2 but it is also the dose approved for the treatment of acute  
3 pain. The dose of naproxen 500 mg b.i.d. is the maximum  
4 labeled dose for chronic use in osteoarthritis and  
5 rheumatoid arthritis, and the label states that a 1500 mg  
6 dose can be used for short term in OA and RA. Rofecoxib is  
7 not currently labeled for use in rheumatoid arthritis. The  
8 anticipated dose by the sponsor's studies would be 25 mg,  
9 but studies to support the safety of rofecoxib in rheumatoid  
10 arthritis have not been submitted to the agency.

11 [Slide]

12 Why the 50 mg dose? Well, the agency suggested or  
13 required this dose, twice the upper limit of their chronic  
14 dose, for both celebre and Vioxx, and the idea was to get a  
15 safety margin because if the product is perceived as being  
16 safer in the GI system, that organ-specific safety may be  
17 interpreted by some as general safety. Therefore, it is  
18 important to know what happens when patients go higher or  
19 above the dose that is recommended. And, we are aware of  
20 the dose creep phenomenon in chronic painful conditions.

21 The rofecoxib dose, as I said, is approved for the  
22 treatment of acute pain. The label states, under usage and  
23 administration, that Vioxx has not been studied for more  
24 than five days in pain studies. However, there is no limit  
25 for the use of the 50 mg dose and we may assume that some

1 patients will take it for longer than five days.

2 [Slide]

3 In fact, we do have some postmarketing usage data,  
4 data provided by IMS Health from May '99 to September 2000,  
5 and of a total of approximately 13 million drug appearances  
6 in that data base, 650,000 were for the 50 mg trend and, of  
7 those, 21 percent were for more than 30 days. Therefore, we  
8 do have evidence that people take the 50 mg dose for longer  
9 periods than they are supposed to.

10 [Slide]

11 Regarding the population, this was a population of  
12 patients with RA and 70 percent of the patients were women.  
13 The median age was 58, and approximately 56 percent were on  
14 concomitant corticosteroids and, very important, an  
15 exclusion to this protocol was that low dose aspirin was not  
16 allowed. Patients on low dose aspirin were not supposed to  
17 stop to get into the trial. They were just not included.  
18 And, any patient deemed by the investigator to require  
19 prophylactic aspirin or anticoagulation at the time of  
20 screening was excluded.

21 [Slide]

22 I have moved to the next slide but I would like to  
23 make the point that that exclusion actually takes out a  
24 substantial number of patients ion the target population of  
25 osteoarthritis and rheumatoid arthritis who will be

1 candidates for cardiovascular prophylaxis.

2           Regarding endpoints, this was a safety study. It  
3 had organ-specific endpoints and those will be discussed by  
4 Dr. Goldkind. The study was powered to detect a difference  
5 in GI specific endpoints but also included prespecified  
6 analysis of routine safety parameters and NSAID-related  
7 events, such as renal-related, liver-related, edema etc.

8           [Slide]

9           This was not an efficacy study. It was not  
10 designed as an efficacy study. It was a non-flare design.  
11 Change in disease-modifying antirheumatic drug therapy,  
12 systemic and intra-articular corticosteroids were allowed,  
13 and rescue analgesia with acetaminophen and non-NSAID was  
14 also allowed at the investigator's discretion. Therefore,  
15 it is not surprising that at the end there were no major  
16 differences in efficacy endpoints.

17           Also, some efficacy endpoints were included, such  
18 as patient and physician global assessment and modified HAK  
19 and the dropouts due to lack of efficacy, however, there was  
20 no measurement of swollen joints, tender joints, ESR/CRP --  
21 those standard measurements in any rheumatoid arthritis  
22 trial for efficacy.

23           [Slide]

24           The major issues that we would like to discuss  
25 today are the generalizability of the gastrointestinal

