

Committee Questions to Merck (Etoricoxib), Novartis (Lumiracoxib) and Dr. Villalba (FDA)

JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

February 16-18, 2005, Hilton Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland.

Highlights.....	1
Etoricoxib Discussion:	1
Lumiracoxib Discussion	4
Discussion of FDA Presentations	5
Presentation Text.....	6

Highlights

Etoricoxib Discussion:

- **NON-US LABELING CHANGES FOR ETORICOXIB:** Dr. Crawford asked what specific revisions in labeling are being made for etoricoxib in non-US markets. Dr. Curtis (Merck) that this will reflect a CHMP-mandated class-wide contraindication in heart failure, ischemic heart disease and cerebrovascular disease. In addition, etoricoxib will have a non-class-wide contraindication in patients with hypertension whose blood pressure has not been adequately controlled". Later Dr. Dworkin asked how the CHMP defined the "class". Dr. Erb (Merck) said that the class is "the coxibs, lumiracoxib, celecoxib, and etoricoxib, and valdecoxib".
- **DICLOFENAC COMPARATOR FOR NEW MERCK ETORICOXIB STUDIES:** Dr. Wood asked what studies Merck would do to get US approval. Dr. Curtis said Merck would proceed with the EDGEII and MEDAL comparisons with diclofenac. Dr. Wood said since diclofenac appeared to be a COX-2 selective drug also, "I am not sure what that will teach us". Dr. Curtis said that diclofenac is "probably the NSAID used most worldwide currently". Dr. Fitzgerald said that diclofenac could be considered as a "surrogate for Celebrex" in the "continuum" of COX-2 selectivity and increased cardiovascular risk, and accordingly these trials would be "very useful" as a comparison of a relatively selective versus a highly selective COX-2 inhibitor.
- **NON-INFERIORITY CRITERIA:** Dr. D'Agostino asked about what would be adequate to be considered a "non-inferiority" trial of etoricoxib.

Dr. Curtis said that this would be the combined data from three trials (EDGE, EDGEII and MEDAL) which would provide a minimum of “635 confirmed thrombotic events”. Dr. D’Agostino asked if people on aspirin in these studies would be part of the non-inferiority evaluation. Dr. Curtis said that “the primary analysis will be based on all patients whether they are on aspirin or not”. Dr. D’Agostino suggested that he would “get rid of” the aspirin users, who don’t have the same hazard as non-aspirin users and “are confounding things”. Dr. Schiffenbauer agreed that aspirin use could reduce the signal of increased cardiovascular risk.

- **META-ANALYSIS OF TWO ETORICOXIB STUDIES VERSUS NAPROXEN:** Dr. Gibovsky asked if etoricoxib would be superior to naproxen in a meta-analysis of the two naproxen studies, only one of which showed “superiority”. Dr. Curtis said that “it would be speculative to talk about combining the results”.
- **NAPROXEN SHOULD NOT BE SEPARATED FROM OTHER NSAIDS IN POOLED COMPARATOR ANALYSIS:** Dr. Shafer said that the data did not support breaking out the etoricoxib comparators into naproxen as a separate group and all other comparators. The results in the etoricoxib trials versus naproxen are similar to those in the rofecoxib-naproxen comparisons but any beneficial effect of naproxen is “certainly nothing of the magnitude” needed to explain a “1.5, 1.7 risk relative to naproxen”. The naproxen manufacturers in their own

presentation ‘felt that naproxen did not have the cardio-protective effects that you have attributed to it’. He asked if we are “not actually seeing a very solid signal for intrinsic increased cardiovascular toxicity with the COX-2 antagonists?” Dr. Curtis did not answer this question directly but said “We have now seen qualitative differences in cardiovascular outcomes against naproxen with three different COX-2 selective inhibitors: rofecoxib, etoricoxib, and lumiracoxib.”

- **NAPROXEN+OMEPRAZOLE AS COMPARATOR:** Dr. Wood asked why Merck did not choose to compare etoricoxib to a combination of naproxen and omeprazole which could reduce the GI toxicity of naproxen. Dr. Curtis said that “we have seen data that suggests even when you add a PPI to an NSAID, there is still room to improve from a GI safety perspective”. Dr. Wood said “You saw that naproxen beats your drug. So, you decided to pick one that didn't look like it would That doesn't make any sense.” He said that randomized trials showing more cardiovascular toxicity than with placebo means that it is not enough to pick a comparator that may be comparable in cardiovascular toxicity. It sounded to him that “we are going into this study saying that we know and believe that the drug will produce a cardiovascular signal, we are just trying to work out if it's better or worse than diclofenac.” Dr. Curtis said that the MEDAL study would help to answer the question of “how big” is the class of drugs that increase cardiovascular toxicity.

- **NAPROXEN MORE RELEVANT THAN DICLOFENAC TO U.S. PHYSICIANS:** Dr. Bathon said that “naproxen is the most widely prescribed NSAID in the U.S. and the most relevant to our practice, whereas, diclofenac has much more hepatotoxicity especially in RA patients where methotrexate is co-administered”, so that it would “have added a lot more to our clinical practice management to see another big trial against naproxen plus you could have added these results to your prior trials and had more power to assess the effect of naproxen versus etoricoxib with all of your trials combined”.
- **ETORICOXIB DICLOFENAC STUDIES ALREADY FULLY ENROLLED:** Dr. Reicin (Merck) commented that the “studies are fully enrolled and ongoing. I can't disagree with you that the idea of doing a naproxen plus PPI study versus a COX-2 inhibitor isn't a good idea and isn't an important question. Unfortunately, we didn't design that study. We designed this one...” and “it will provide beneficial safety data to see what a selective COX-2 inhibitor looks like versus a non-selective inhibitor, albeit not as non-selective as naproxen.”
- **FDA DID RECOMMEND ADDITIONAL COMPARATORS TO MERCK:** In response to a question by Dr. Platt, Dr. Schiffenbauer said that FDA “recommended strongly” to Merck “that additional agents” (other than diclofenac) “be studied to get a better handle on the true cardiovascular risk” with etoricoxib.
- **UNDERLYING CV RISK IN MEDAL STUDY:** In response to a question by Dr. Farrar about “the difference in the underlying risks between some of these different comparisons”, Dr. Curtis said that in the MEDAL study is 75% osteoarthritis, 50% hypertensive, and 12% “documented atherosclerotic cardiovascular disease”.
- **IS THERE A CONTINUOUS GRADATION OF RELATIVE RISK ACROSS DIFFERENT LEVELS OF BASELINE CARDIOVASCULAR RISK?** Dr. Farrar asked Dr. Fitzgerald to comment on whether relative risk is increased in all groups with cardiac risk factors or whether it is restricted to those with “release of active agents from the surgical procedure”. Dr. Fitzgerald said that it was “conjecture” but that “as we move away from that extreme” (CABG surgery) “through what we call ‘heightened’ cardiovascular risk, there is probably a continuum of predisposition” based on the “predisposition” to such factors as hemostatic activation and hypertension induction. Dr. Wood pointed out that there was increased risk “even in the people with no history of cardiovascular disease”.
- **IF COX-2 DRUGS PROMOTE ATHEROGENESIS, FIVE-YEAR TRIALS MAY BE NEEDED:** Dr. Nissen expressed concern that if the COX-2 drugs are “promoting atherogenesis” randomized trials may have to be of 5 years duration, and you would not be able just to increase the “sample size in order to shorten the duration”. Dr. Curtis said “I am not going to disagree” but that arthritis trials tend to have 40% dropout by 1 year and an additional 10-20% yearly thereafter, which

would make a valid 5 year study very difficult in this population.

- **MORTALITY APPEARS INCREASED IN EDGE ETORICOXIB STUDY:** Dr. Fleming said that in the EDGE study (with a 3:2 randomization) APTC events were 43 versus 12 which is “certainly well outside of unity”, and that the mortality results shown are “difficult to really see in this scale” but mortality appears increased and “it looks as though ...you are looking at about a 1.5 relative risk on

mortality across the aggregate of these data.”

- **ETORICOXIB IS MORE COX-2 SELECTIVE THAN VIOXX:** Ms. Malone asked for a “simple answer” about how different etoricoxib was from Vioxx. After some clarification of the question, Dr. Curtis said that etoricoxib is more selective for the COX-2 receptor than Vioxx but that “in the dose range that these drugs are used, they all selectively inhibit the COX-2 enzyme and do not inhibit COX-1”.

Lumiracoxib Discussion

- **LUMIRACOXIB RISK RATIO A FUNCTION OF THE COMPARATOR:** Dr. Hennekens suggested that the different risk ratios for lumiracoxib versus ibuprofen of 0.76 and versus naproxen of 1.46 could be a result of the different comparators and of a protective effect of naproxen.
- **POSSIBLE INCREASED CARDIOVASCULAR RISK OF IBUPROFEN:** Dr. Abramson referred to a slide shown by Dr. Villalba (FDA) in which she suggested that lumiracoxib “behaved differently” in the two components of the TARGET study. He does not think this is a valid interpretation. He suggested that lumiracoxib could be worse than naproxen because of some mix of naproxen protection and lumiracoxib toxicity, but that the comparability of lumiracoxib and ibuprofen suggests that “ibuprofen has some risk attached to it”. Dr. Villalba agreed with his point.
- **REASON FOR 2-FOLD DIFFERENCE IN CV**

LUMIRACOXIB EVENT RATES IN TWO COMPONENTS OF TARGET: Dr. Bathon asked why the two components of the TARGET trial had a 2-fold difference in cardiovascular event rates on lumiracoxib despite “the same inclusion and exclusion criteria”. Dr. Matchaba (Novartis) responded that these differences “could be chance” but could be related to the different countries contributing sites, to differences in the time scales for the two components, or to differences in baseline cardiovascular risk.

- **INCLUDING SILENT MIs IN TARGET CV EVENT DEFINITION OBSCURES 3-FOLD INCREASE WITH LUMIRACOXIB:** Dr. Cryer suggested that some of the differences between TARGET and previous COX-2 outcome studies could be related to not using “fully adjudicated definite events” in the TARGET study. If you exclude silent MIs and just look at clinical MIS there is “an apparent 3-fold

increase with lumiracoxib for clinical MIs compared to NSAIDs, which dramatically differs from your other conclusion.” Dr. Matchaba said that all events were prospectively adjudicated. Dr. Cryer said that he was asking for data that “excluded the probable”. Dr. Farkouh (Novartis consultant) responded that “probable was an element or a degree of definite”. Dr. Cryer said “With all due respect, I will ask the question a third time”. Dr. Farkouh said “we did not feel there was any distinction between the two of them, so we did not mandate that.” Dr. Matchaba added that when you look at silent MIs alone, the same lumiracoxib-naproxen and lumiracoxib-ibuprofen trends are seen.

- **SUPERIOR GI SAFETY PROFILE OF LUMIRACOXIB MAY BE BECAUSE PATIENTS WERE AT LOW GI RISK:** Dr. Cryer also suggested that the superiority in GI safety might have been because of a “low GI risk population” since we “know that the relative risk of COX-2 specific inhibitors to have a GI benefit is

greater in a population that has low GI risk”.

- **WEIGHTING OF FAVORABLE GI AND UNFAVORABLE LUMIRACOXIB CV EVENTS:** Dr. Fleming said that Dr. Matchaba’s comparison of favorable GI events with unfavorable CV events in the naproxen comparison was misleading. His calculation was that for GI events “in terms of per 1,000 people, there are about 7 cases that are prevented” whereas for CV events “for 1,000 people, there are 3 of those cases”. This way of looking at the data changes “a clear positive” to “much less clear, if not clearly negative”. Dr. Matchaba said that “it is an attempt on our part that using this unvalidated method for the first time and prespecifying it and stacking up the primary endpoints, what does the picture look like relative to comparators in the same study?” Dr. Wood said “And a GI bleed is not the same necessarily as a stroke. They don’t compensate for one another. That is not a criticism, it is just a fact.”

Discussion of FDA Presentations

- **APTC DEFINITION:** Dr. Hennekens coauthored the APTC criteria which “prespecified non-fatal MI, non-fatal stroke, and all vascular deaths as the combined endpoint” but excluded silent MI. He thinks that Merck’s definition is correct and that Novartis and FDA have used a different one.
- **DEFINITION OF “CLASS” EFFECT:** Dr. Abramson also asked what Dr. Villalba meant by “class effect”. Dr. Villalba said that she was referring to the “entire class ... with different degrees of selectivity within the NSAID class”.

Presentation Text

DR. WOOD: We have three tasks that we need to get through this afternoon, so pace yourselves as you think about that, colleagues. We have got to deal with the questions and the issues that came up from the last two sets of presentations. We need to have Dr. Furberg address the Pfizer issues that he raised yesterday and give Pfizer the chance to respond to that, and we will come back to that in a second. The third we need to do is start to address the questions that the FDA prepared for us. So, there are three tasks we need to get through. It is just after five past 3:00, and we need to get started on that. Let's begin with the questions for the speakers on etoricoxib. Oh, Dr. Hennekens first.

DR. HENNEKENS: In the 1970s, I was in Oxford with Richard Peto. I had the privilege to help him put together the APT Collaboration. We prespecified non-fatal MI, non-fatal stroke, and all vascular deaths as the combined endpoint. We specifically excluded silent MIs in the first cycle in '88 and the second with Rory Collins leading in '93, and the third with Colin Baigent, now called the ATT. So, Merck, in my view, has used the correct APT now ATT definition. It is Novartis and the FDA that are at variance with what the APT definition. I had a question for the FDA presenter. One of the things Peto told me is if you torture the data enough, they certainly will confess, but with that as a background, the lumiracoxib comparison versus ibuprofen is 0.76, against naproxen it's 1.46, and the conclusion is that the drug is behaving differently in the two studies. Well, the alternative hypothesis based on the evidence we have seen so far is that there may be a

protective effect of naproxen and perhaps some harm of the shorter acting NSAIDs, a hypothesis supported by the basic science showing some deleterious actions of all the NSAIDs, but this potential beneficial effect on platelets of the longer acting NSAIDs. So, I think it may not be necessarily true that we need to conclude that this drug is behaving differently in two studies with two very different comparators.

DR. VILLALBA: My conclusion was that I really don't know what to make of it, and that is why I need the opinion of other people here. The conclusion really was that this probably a class effect, this is a very heterogeneous class, and you have all the degrees of selectivity there. So, that is what we need to determine.

DR. WOOD: We have got Dr. Stephanie Crawford.

DR. CRAWFORD: Thank you. I would like to ask Dr. Sean Curtis to please come to the microphone if you are in the room. Dr. Curtis, this morning you stated that in global markets, Merck is currently revising its labeling for etoricoxib to address new safety information relative to the safety of selective COX-2 inhibitors, so I am intrigued. In what manner, specifically, what is the sponsor stating in its revised labeling worldwide on the safety of this product?

DR. CURTIS: We participated in the European referral. It has been basically a referral process for all the COX-2 inhibitors, and that is actually just wrapping up, as you know. I, of course, have been here, but I am aware of now

that there has now been wording for the label that talks--and this is basically class labeling in terms of contraindications--but I think really what it boils down to, you know, we have been informed from the CHMP that there will now be a class-wide contraindication for all coxibs related to congestive heart failure. It was previously classed as 3 and 4, it has been extended to Classes 2 through 4. In addition, there will be contraindications in patients with established ischemic heart disease and/or cerebrovascular disease, so that will be class contraindication, class labeling. In addition, for Arcoxia or etoricoxib, there will be contraindication in patients with hypertension whose blood pressure has not been adequately controlled. So, that is obviously new information as of today, and that is, in essence, what I mean by working with the regulators, based on new and evolving information, to come up with product labeling that accurately and adequately reflects current knowledge.

DR. WOOD: I think she was asking you--which I suspect is going to be the committee's focus the rest of the afternoon for both the sponsors, for the committee at least to decide what the committee would need to see before they approve new drugs like this--I think what Dr. Crawford was asking was what were the studies you were proposing to do to do that. Is that right, Dr. Crawford?

DR. CURTIS: Could you restate the question? I couldn't hear you.

DR. WOOD: I think the question was what studies were you proposing to do, that you thought would help get this drug approved in the future.

DR. CURTIS: As I reviewed through my presentation, we feel the underlying safety information that is most relevant to ensure that we are all comfortable with the safe and effective use of the drug, is to proceed with the studies that I outlined this morning, namely, EDGE II and MEDAL, which are, as I reviewed, opportunity to assess the long-term safety of the compound in contrast to traditional care, namely, diclofenac. I reviewed the reasons why we chose diclofenac. There is pluses and minuses of the comparators, but that is our primary method to further assess the compound at this point in time.

DR. WOOD: Put on slide 31 again, would you. That was the slide that showed the relative potency on the COX-1 and COX-2. Basically, I think Dr. FitzGerald said earlier that he saw this as 'rofecoxib lite' or something. So, given that you presumably wouldn't have expected to see a difference between your new drug and rofecoxib, it seems like you picked the next best thing to do as your comparator. Naproxen is up there higher up, and you picked the one that was closest to rofecoxib to make your comparator, so the chances of seeing a difference seemed to me extraordinarily small, and I am not sure what that will teach us.

DR. CURTIS: Could we go to slide 1115, please. The slide that I just showed as part of the core presentation was the weighted mean average. I did also want to point out that diclofenac here, what is plotted here is again at steady state and a percent inhibition from baseline again of a COX-1 assay looking at platelet, thromboxane, B2. This is a plot of inhibition both at peak

and at trough of the exposure in the blood. You see diclofenac at trough has about 60 percent inhibition of thromboxane, but at peak, achieves levels that are close to 90 percent, so there is some variability in the degree of thromboxane inhibition throughout the dosing interval. I went through the reasons why. I showed some clinical data, too, that did suggest that at least from a GI tract perspective, which, of course, is ultimately one of the key safety endpoints, that there is a way to differentiate diclofenac from other NSAIDs--excuse me--from what we consider COX-2 selective inhibitors. I showed you data with valdecoxib and rofecoxib. In thinking about other comparator choices, there are limitations to the use of the other NSAIDs that I reviewed, and I think fundamentally one needs to keep in mind that diclofenac at this point is, in essence, probably the NSAID used most worldwide currently. So, you know, in acknowledgment of the limitations of choosing any single individual comparator, and in acknowledging some of the limitations that were reviewed perhaps in the TARGET study even, where if you do start to do sub-studies, you do run the risk of showing different estimates even with one comparator, even with the same compound. We felt that doing a large study of the magnitude that I described for MEDAL against one comparator, and I reviewed the reasons why we chose diclofenac, was as reasonable a choice given all the alternatives.

DR. WOOD: Garret, are you still here? Maybe the question to him is supposing that study turns out with no difference, are you going to hear from him that he doesn't believe that tells you anything because it is just another COX-2

selective drug, is that what we are going to hear, Garret?

DR. FITZGERALD: I would take a slight different tack. We have heard the words "continuous variables" used quite a lot, and I think it is a continuum from as one extreme, very selective, very long-lived drugs, going through shorter lived, less selective drugs through to very non-selective drugs. I would guess that the ease of detection and the size of signal would move across that spectrum from being very large to being very small or undetectable. So, I won't reiterate the reasons why. I think diclofenac resembles remarkably Celebrex with respect to selectivity, and I would view this trial as actually a very useful trial, beginning to address for us information that we need to know. I would cast it as a within COX-2 selective trial in that respect. It is like we have a surrogate for Celebrex. We saw a lot of little trials with many flaws in the blood pressure arena yesterday, setting up Celebrex against rofecoxib with arguments about timing of dosing, and so on. Well, here the rubber meets the road. We actually addressed the question of whether a commonly used, relatively selective drug, diclofenac, stacks up in a way that segregates from a longer lived, much more selective drug, etoricoxib, so I think it does provide useful information in that regard, although I might cast the reasons for why I think it is useful in a slightly different way.

DR. WOOD: Any other questions? Dr. D'Agostino.

DR. D'AGOSTINO: This is both for Joel and Sean. You raised the question, Sean, about doing a non-inferiority study, and I am wondering--that certainly will be a

discussion that we will have--and I am wondering if you realized the implications of that. When you look at, for example, slide 44, in your presentation, and you look at the EDGE study, was the EDGE study a non-inferiority trial?

DR. CURTIS: I actually wanted to clarify something that Dr. Schiffenbauer mentioned. So, the answer is no. The non-inferiority criteria that I identified in the presentation is based on cardiovascular safety data accrued from three studies: EDGE, EDGE II, and MEDAL. So, the cardiovascular non-inferiority criteria is to be applied to the minimum 635 confirmed thrombotic events that will accrue from three studies.

DR. D'AGOSTINO: From the three studies, not one at a time.

DR. CURTIS: That's correct, but I am providing you data that is coming available, and EDGE had finished, and it is an important piece of information.

DR. D'AGOSTINO: That is comforting in terms of what is possible, but just to point out that on that result, that would not be very positive for you if you did the 1.3. You would actually, in that case, say that the comparator could be better. I mean that would be a conclusion in that study. I don't want to go into the details of that, but one has to be very careful when they go the non-inferiority route, and we will talk about that more. This slide frightened me a bit. The other is if you do go the non-inferiority route, what about the inclusion of the aspirin individuals, it probably won't be a constant hazard in the sub-groups, but what will happen then with your non-

inferiority. This was raised by Joel, and I would like an answer. I would love to hear what your answer is.

DR. CURTIS: Aspirin, of course, it is hard to win with that, and I will tell you why. On the one hand, you want to include patients with a range of baseline risk, and certainly one criticism of some of the studies is that patients with cardiovascular risk have not been included in these studies. Both us and the FDA felt it was important, as the data provided to included patients with baseline cardiovascular risk, but, of course, those patients should be on aspirin. So, we, of course, allow patients to be on aspirin as per clinical guidelines. As I mentioned, we expect about 30 percent of the total patient cohort in the cardiovascular analysis will be on aspirin. But I want to be clear, the primary analysis will be based on all patients whether they are on aspirin or not.

DR. D'AGOSTINO: But are you going to be assuming in the 1.3 that the hazard ratio will be the same within that subgroup, but just that it will be a different level of absolute risk? We will talk about those things, but those are serious implications. I would have to have a study design where the very first thing you do is say, well, gee, I couldn't do what I set out to do, I have to look at subsets, namely, I have to get rid of the aspirin users because they are confounding things. Was that the concern that the FDA is having?

DR. SCHIFFENBAUER: Yes, as I expressed, in the non-inferiority design where we don't have the placebo background, this would be a maneuver to make the two groups look more

similar. I mean if you extrapolate it to 60 percent or 80 percent aspirin use, I think the two groups would look almost identical, so you would end up having to look at subsets, that is true.

DR. WOOD: Dr. Abramson.

DR. ABRAMSON: Yes, I have a question for Dr. Villalba

DR. WOOD: Can we just deal with the first presentation first.

DR. ABRAMSON: I am sorry. Then, I will wait.

DR. WOOD: Dr. Gibofsky.

DR. GIBOFSKY: Dr. Curtis, I have a concern about the selective emphasis of data being presented in seeming replicate trials. If we go to slide 10, for example, and again in slide 46, you commented that etoricoxib was superior to naproxen in one of two pivotal studies, but similar in the other study, and based on that one study, you have used the term "superiority" at least twice in your presentation. I guess I am kind of wondering, if you did a back of the envelope calculation, like Dr. Fleming did yesterday afternoon when we were discussing two polyp trials, one of which we gave more focus to I think than the other, would you still be able to make this claim of superiority based on the meta-analysis with both trials?

DR. CURTIS: My point in highlighting the efficacy data was, of course, not to talk about a claim of superiority. The purpose was to provide data that provides you and all of us an opportunity to look at both the risks and the benefits of the compounds, and the data in RA

were compelling, and I fully disclosed results from both studies. Furthermore, the data, these really were the first studies that we are aware of that showed a statistically significant difference. So, my point was again in the context of an overall risk-benefit assessment, to claim--to not claim, but to show the data for this compound at the doses that were studied provide a level of efficacy that certainly should be part of the consideration. I certainly would not be claiming any sort of label claim or anything like that, because we are not here to talk about such things.

DR. GIBOFSKY: I take your point, but specifically, if you combine the second study with the first, would you use the word "superior" to naproxen, or would you use the word "equivalent" to naproxen?

DR. CURTIS: I can only talk about a clinical study within the context of that clinical study where patients were randomized evenly between treatment arms. I think it would be speculative to talk about combining the results.

DR. WOOD: Dr. Shafer.

DR. SHAFER: If you can go to slide 19, and we see here that once again the confidence bounds around the three groups do not really justify the breaking out of naproxen, it would appear to me, as a separate group. Now, go to slide 44. Once again you have broken out naproxen as a separate group although it is not clear that the confidence bounds would support that either. So, we have a pattern where you are constantly seeing a worse outcome compared to naproxen, and similar to rofecoxib, where the same signal came up, you asked, I think, or

you mean to imply to us that naproxen is intrinsically different, but we have heard multiple experts over the course of the last day and a half tell us that they don't believe that naproxen is intrinsically different. We have seen observational trials in which there may be a modest effect of naproxen, but certainly nothing of the magnitude to explain a 1.5, 1.7 risk relative to naproxen that you have seen in your data, and even the sponsors themselves, Roche and Bayer, in their presentations, felt that naproxen did not have the cardio-protective effects that you have attributed to it. So, first, I am disturbed that your primary analysis isn't versus NSAID comparisons, all NSAIDs, and then as a subgroup, you compare naproxen out. Instead, you pull naproxen out and ask us, I mean the implication almost is that we should dismiss it, because it's naproxen, and then look at everything else. It concerns me that we aren't primarily looking at all NSAIDs as the comparison group. Secondly, at this point in time, do you truly believe that naproxen and the postulated cardio-protective benefits of naproxen truly explain the difference that you are seeing, and that we are not actually seeing a very solid signal for intrinsic increased cardiovascular toxicity with the COX-2 antagonists?

DR. WOOD: And while you are answering that question, tell us why the right study wouldn't be to do a naproxen with omeprazole versus your drug. I mean you obviously believe naproxen beats the drug, right? And the only advantage of the drug over naproxen is a GI benefit. Supposing omeprazole gave you the GI benefit and you still had the cardiovascular benefit, wouldn't that be the optimal therapy? And why, given your data here, did you choose to go

with the drug that has less benefit than naproxen? I still don't understand that.

DR. CURTIS: I am going to answer your second question first. Naproxen clearly is a very effective drug, however, as we heard repeatedly today, patients have different responses to therapies. Again, the reason people with arthritis take drugs is so they can have some relief. Not everybody responds to naproxen. So, I think naproxen clearly is a very logical choice for many patients, but there are going to be patients who do not respond to naproxen, and when you factor in GI risk, adding a PPI certainly would appear to likely to mitigate some of the risk, but you are still going to be left with patients who don't respond to naproxen, who still are going to have a residual GI risk, and we have seen data that suggests even when you add a coxib or a PPI to an NSAID, there is still room to improve from a GI safety perspective. So, I think that as a therapeutic option, selective COX-2 inhibitors, including etoricoxib, still have a role. As to why we chose not to use naproxen as the comparator in our outcome study, I reviewed the reasons. We have now seen qualitative differences in cardiovascular outcomes against naproxen with three different COX-2 selective inhibitors: rofecoxib, etoricoxib, and lumiracoxib. We felt that doing an outcome study against naproxen, we would likely replicate that observation again. We felt it was important to accrue additional data against another traditional NSAID that was used widely around the world to get a more firm estimate of what the cardiovascular risk looked like against another NSAID.

DR. WOOD: You looked at that data. You saw that naproxen beats your drug.

So, you decided to pick one that didn't look like it would--because it is as selective as your drug is--and you are going to come back with that data and say wow, it doesn't produce any cardiovascular signal because it's the same as diclofenac. That doesn't make any sense.

DR. CURTIS: Again, I think it is important to remember that the qualitative differences that were observed against naproxen were being seen at the same time that no differences were being observed with non-naproxen NSAIDs, and in a time frame like a year for which a difference from placebo with COX-2 inhibitors has not been appreciated. So, I think all that data, to me, continues to say that there is something different about naproxen. I can't quantify that, I don't think the data allow that, but there clearly appears to be something different about comparisons to naproxen to the other NSAIDs.

DR. WOOD: I understand that, but the issue that has changed since our initial studies with naproxen is that we now have three randomized trials against placebo in which placebo beat the drug. So, using an active comparator that you have chosen to match in terms of cardiovascular adverse events, etoricoxib, isn't acceptable in terms of showing that the drug doesn't have an effect on cardiovascular mortality or morbidity. It might have been acceptable in the days when you believed that naproxen was beneficial and that that was the total explanation, but by your own admission, you don't believe that anymore.

DR. CURTIS: So, if I understand the question, you are asking why we are not

doing a large outcome study against naproxen.

DR. WOOD: I guess I am asking you what you are going to learn from the diclofenac study. You are certainly not going to be able to say that this drug does not produce cardiovascular problems given that you have deliberately chosen a drug that looks as similar to etoricoxib as you can get, and from your earlier studies, namely, this one, you have seen that it does produce a difference with naproxen, and it doesn't appear to produce a difference with this, and it has got a very similar pharmacology. So, if you can imagine an imputed placebo arm here, and given what we know about placebo, you would predict that this drug would do worse than placebo, and you won't be able to exclude that from the study you are designing.

DR. CURTIS: The data that are emerging, that we have all seen the APPROVe data, we have all seen the difference against celecoxib in the APC study, to us, that suggests a class effect. I have showed you our placebo-controlled data for etoricoxib, it's very limited. With that being said, the class effect related to COX-2 inhibition, we would presume extends to etoricoxib, and, to us, the real clinical question is in patients who require chronic treatment, what is the cardiovascular safety against a standard of care, and for the reasons I reviewed, we chose diclofenac.

DR. WOOD: So, let me be sure I understand. So, we are going into this study saying that we know and believe that the drug will produce a cardiovascular signal, we are just trying

to work out if it's better or worse than diclofenac.

DR. CURTIS: No, I think what we are asking is--

DR. WOOD: Well, that is what you just said, isn't it?

DR. CURTIS: If I could rephrase what I said, I think what we are saying is we are suggesting there is a class effect, and we are not sure how big the class is, and we feel that the MEDAL study will help provide information to address that specific question, whether cardiovascular safety for selective COX-2 inhibitor is the same or different than that of a traditional NSAID, one that is the most widely used NSAID around the world currently.

DR. WOOD: Okay. Dr. Bathon.

DR. BATHON: I was going to say much the same thing. I have the same concerns about this especially since naproxen is the most widely prescribed NSAID in the U.S. and the most relevant to our practice, whereas, diclofenac has much more hepatotoxicity especially in RA patients where methotrexate is co-administered. So, I think it would have added a lot more to our clinical practice management to see another big trial against naproxen rather than diclofenac, plus you could have added these results to your prior trials and had more power to assess the effect of naproxen versus etoricoxib with all of your trials combined, but now, since you are using diclofenac, you don't have that extra power.

DR. WOOD: Dr. Reicin.

DR. REICIN: Let me just make one comment, and as all you start to talk about designing clinical trials, I think you will see, as many of you know, it is quite difficult and you cannot answer every question in every study. MEDAL was started over two years ago, and at that time there was no placebo-controlled data to suggest that COX-2 inhibitor was different than placebo. Obviously, that has changed. The studies are fully enrolled and ongoing. I can't disagree with you that the idea of doing a naproxen plus PPI study versus a COX-2 inhibitor isn't a good idea and isn't an important question. Unfortunately, we didn't design that study. We designed this one, and I think, as Garret said, it will provide information about how big the class is. While some of you may not be using diclofenac, it is the most widely used NSAID in the world, and therefore, I think it will provide beneficial safety data to see what a selective COX-2 inhibitor looks like versus a non-selective inhibitor, albeit not as non-selective as naproxen.

DR. WOOD: Thanks. Dr. Dworkin.

DR. DWORIKIN: Yes, a simple question. You said that the CPMP had come up with class labeling, but you neglected to tell us CPMP defined the class. Is it all NSAIDs, is it COX-2 inhibitors, and if the latter, what drugs were included in that subclass?

DR. CURTIS: I am going to give my understanding as a clinician who has been here for the last 48 hours, but my understanding it is specific to what we consider the selective COX-2 inhibitors - celecoxib and etoricoxib, and that that is how the class is being defined currently.

DR. DWORKIN: So, those two drugs, but not, for example, meloxicam.

DR. CURTIS: Dr. Erb, would you like to comment on any additional agents?

DR. ERB: Yes, Dennis Erb from Regulatory Affairs. The CHMP is included in the class, what we have been referring to today as the coxibs, lumiracoxib, celecoxib, and etoricoxib, and valdecoxib.

DR. WOOD: Dr. Platt.

DR. PLATT: More on the history of the choice of comparators. Dr. Schiffenbauer, could you tell us more about the conversations between the agency and the sponsor around the choice of comparators? Your comments and the materials you presented to us suggested that you had reservations about that choice.

DR. SCHIFFENBAUER: Yes, we had extensive discussions with the sponsor. At the time we appreciated the difficulties doing a placebo-controlled trial, but we had requested--and I can't quote you whether it was additional comparators or comparator--but we had recommended strongly that additional agents be studied to get a better handle on the true cardiovascular risk.

DR. PLATT: Was there discussion about naproxen as a comparator?

DR. SCHIFFENBAUER: Not specifically other than to mention that we recommended additional comparators.

DR. WOOD: Dr. Farrar.

DR. FARRAR: One of the things that strikes me about all of the studies that we have been looking at, and perhaps most in the comparison of studies that we are still waiting for some data on, namely, APC and PreSAP, is the difference in the underlying risks between some of these different comparisons. I noticed that in your particular study, the cardiovascular risk, you felt that 38 percent--I think that was the number--that in your slide you had 38 percent at an increased risk of cardiovascular disease with 24 percent on aspirin and 10 percent of them as being diabetic. I just wondered if you could comment on what the mix of the MEDAL study is likely to be or is. I mean you certainly would have the data at this point.

DR. CURTIS: Yes. 1103, please. The MEDAL study population is, as I mentioned, both OA and RA patients, so approximately 75 percent of the patients have OA and about a quarter have RA. What is represented here are the risk factors for the cohort, the entire cohort, and it is not dissimilar to what I highlighted for the EDGE study. These are basically baseline medical diagnoses at the time of entry into the study, so about half have hypertension, which is a little higher than the EDGE study, which was about 40 percent, as you see here, the individual cardiac risk factors, and this 12 percent of history, that is documented atherosclerotic cardiovascular disease. The 38 percent that I quoted for the EDGE study was patients with this or two primary risk factors. So, that percentage, if I were to calculate that percentage for this study, it would probably be a little higher than

EDGE, probably about 40, 42 percent. So, these are the patients in MEDAL.

DR. FARRAR: If I could just follow up and ask actually Garret FitzGerald, whether he has any comments on the relative risk of patients who have either high or low cardiovascular risk factors. I mean we know from the study, the CABG study, that patients with very high risk clearly have a marked increased response to these drugs, and whether people who have cardiac risk factors are also in that category, or whether it really is restricted to sort of the release of active agents from the surgical procedure.

DR. FITZGERALD: Well, obviously, the actual information we have relevant to your very important question is conjecture. What we know mechanistically is that what we would expect would be the response to thrombogenic stimuli would be enhanced, as would the predisposition to the other cardiovascular adverse manifestations of this mechanism, namely, hypertension and atherogenesis. So, for example, if a population was enriched in patients with secondary hyperaldosteronism, they would be more prone, on average, to exhibit hypertension in response to an NSAID or particularly a selective COX-2 inhibitor. Similarly, if they were at advanced risk of hemostatic activation, they would be prone to the thrombogenic complications, and I think with the CABG patients, we had an extreme phenotype of excessive hemostatic activation. Now, as we move away from that extreme through what we call "heightened" cardiovascular risk, there is probably a continuum of predisposition that is a mix of predisposition to the

various types of manifestation of this mechanism that could occur. So, we have only crude indicators obviously, and to some extent, as I talked about yesterday, it's in the eye of the beholder as to what defines heightened cardiovascular risk, but on average, the group defined as having higher cardiovascular risk, for example, RA compared to OA, on average would be expected to show a signal easier than in a group with low cardiovascular risk. I mean I would think with this type of study, we may have had a premonition of the outcome from the EDGE result. For example, if we think of these two drugs as defining the limits of a class, just for fun, one could say like in the EDGE results, you wouldn't see a distinction in the hard GI endpoints or the hard cardiovascular endpoints, but what you might see a distinction in is their fringe surrogates, which might be easier to pick up, such as discontinuations because of hypertension or discontinuations because of GI side effects, and that is actually what was seen at the two ends of the spectrum in the EDGE result.

DR. WOOD: But we do know from the APPROVe study that the point estimate, even in the people with no history of cardiovascular disease, which would be the only clinical measure we could reasonably use to distinguish that, it is still substantially greater than 1.

DR. FITZGERALD: Yes, I mean I did try to raise the issue yesterday that how we define underlying clinical substrate is an inexact science, on the one hand, and on the other, that many other factors that we discussed yesterday could play into the likelihood of manifestation of risk at the individual level.

DR. WOOD: Steve.

DR. NISSEN: I want to maybe bring us back to earth a minute and talk about the time horizon for such a trial. I feel compelled to point out that we have got a lot of history in cardiovascular medicine of studying drugs for atheroprotective effects. Those trials are typically not one year or two years or even three years, they are typically five-year studies, and in many of them, let's take a blockbuster class of drugs like the statins. Look at the CARE trial. The CARE trial, the Kaplan-Meier curves didn't diverge at all for two years, and so now we have got a drug here that may be promoting atherogenesis, and so we are going to say, well, we are going to have a 20-month mean exposure, and if it doesn't produce a problem, then, there must not be a problem, and I am not sure that's right. The problem we have is that what has been done here is the sample size has been increased to a large sample size in order to shorten the duration, but that may not be the same as studying a more modest size group of patient for three or four years. It is assuming that the hazard is constant over time, and I am not so sure that it is here. If, in fact, Garret is right, and he has been right about a lot of things, that these drugs are potentially atherogenic, then, an atherogenic intervention may not produce an effect for several years. So, how can you reassure us here that a 20-month mean exposure is enough to allow us to move forward with a drug like this?

DR. CURTIS: I think what you are touching on is--I am not going to disagree--what I am going to point out is the fact that I think running an arthritis study is perhaps different, and I have not

designed outcome studies, cardiovascular, other than this--but to keep arthritis patients in studies is difficult, and that has to do with the treatment of the disease. As the rheumatologists here can speak to, a traditional trial has 40 percent of the patients discontinuing after one year, and another 10 to 20 percent dropout rate every year subsequent, so there are significant practical limitations to keeping patients on study therapy into the time frame that you proposed, Dr. Nissen. So, that is a practical limitation to running arthritis studies.

DR. NISSEN: I just would also point, however, that the patients that we studied initially with these atheroprotective drugs were very high risk secondary prevention patients. These were not low risk people. So, you are going to take a lower risk population and you are going to look for a signal at a 20-month mean duration, and that signal may actually take longer to show up in a lower risk population. So, I am troubled by how long we have to look for with a drug like this before we really can say there isn't a problem. People may take these drugs for a decade. We heard that from people at the microphone here. So, these are some of the things that trouble me about the whole question.

DR. WOOD: I have got a whole list of questions here, but I want to keep us moving here. So, are there any people who have burning questions that they want to torture Dr. Curtis with before we let him off? It has to be specific. We will take Tom, we have not heard from you yet.

DR. FLEMING: Burning?

DR. WOOD: Burning.

DR. FLEMING: There are two or three issues I want to quickly review. You didn't mention in EDGE the new ischemic heart disease or the heart failure, pulmonary edema, cardiac failure. I think the FDA indicated in their review, there was a 25-19, and a 14-6, so basically about a 30 percent relative increase and a doubling in those two, is that your understanding?

DR. CURTIS: The numbers, yes, Dr. Schiffenbauer quoted, those are the correct results, and that information was in your background package.

DR. FLEMING: And then very quickly, your slide 19 and then your slide 25. On your slide 19, do you have the analogous slide for the APTC results? If you don't, my understanding is the relative risks are less favorable than this or more unfavorable, depending on your perspective. They are 1.8, 0.87, and 2.72?

DR. CURTIS: That is correct, yes.

DR. FLEMING: So, essentially, we are looking at with roughly a 3 to 2 randomization in the aggregate, and the aggregation of these events here, we are looking at 43 versus 12, so a pretty substantial excess in the critical APTC measures.

DR. CURTIS: Well, again, as you know, the APT events in total are smaller than these numbers, so your confidence intervals around those point estimates are, in fact, much broader.

DR. FLEMING: But at 43 to 12, they are certainly well outside of unity. The last thing is slide 25. You give the mortality results, but it is difficult to really see in this scale, but it appears that the relative risks are roughly in the range of 1.6 against placebo, also 1.6 against naproxen, and 1.2, and then in addition to that, it is also 1.33 in the EDGE trial. So, it looks as though when you look in terms of relative risks, that you are looking at about a 1.5 relative risk on mortality across the aggregate of these data.

DR. CURTIS: Yes, this slide shows the rate with the confidence interval. I don't have the relative risk.

DR. FLEMING: But those aren't relative rates is my point.

DR. CURTIS: That's correct, these are absolute rates here.

DR. WOOD: So, you are saying this stuff doesn't look it's good for you. Anyone else who has a burning question? Go ahead.

MS. MALONE: It's burning. I would like a simple answer. How much different--now, I heard him call this like Vioxx lite, I believe I heard him say that--how different is this from Vioxx, you know, chemically, and do you see it as a substitute for people who are perhaps taking Vioxx?

DR. WOOD: I think we are talking about diclofenac. It was the comparison to diclofenac which had been referred to.

MS. MALONE: He also did a presentation on etoricoxib. So, can he answer that?

DR. WOOD: You are asking me?

MS. MALONE: No, him. Okay, I am sorry, I thought you had said that about etoricoxib.

DR. CURTIS: Can you clarify the question, please?

MS. MALONE: I am just wondering how the compound in etoricoxib compares to Vioxx.

DR. WOOD: You mean chemically?

MS. MALONE: Yes, but in simple terms.

DR. CURTIS: The human whole blood assay, if that is your specific question, the human whole blood, which is sort of the gold standard, that shows a degree of COX-2 selectivity that is greater for this drug, but in the clinical dose range, etoricoxib, just like rofecoxib, just celecoxib, just valdecoxib, are selective for the COX-2 enzyme in the clinical dose range, so in that regard, they are similar. Does that answer your specific question?

MS. MALONE: I am just wondering, you know, I have heard people say that Celebrex or Vioxx was much more selective than Celebrex and Bextra, and where does this fit in, in that scheme?

DR. CURTIS: Again using the human whole blood biochemical assay, this drug would be considered more selective, but I think the key concept, at least for me as a clinician, is that in the dose range that these drugs are used, they all selectively inhibit the COX-2 enzyme and do not inhibit COX-1.

DR. WOOD: Let's move on to the next set of presenters and let Dr. Curtis off the hook. Thank you very much. Are there questions for the Novartis presenters from the committee? Some of the people who are still waiting for the questions, we will begin with them if they want to start with the other ones. Dr. Abramson had one, I know, and we punted.

DR. ABRAMSON: That was the TARGET presentation by Dr. Villalba. I would like to just throw slide 9 up, if we could, and follow up on a point that Dr. Hennekens made when we started this session. In that slide, you combined the two component studies of TARGET and again said that lumiracoxib behaved differently in the two studies, but I think that is probably incorrect to put up a slide like that. It is like putting up a CLASS and a VIGOR slide together, because these were, as I understand it, separate studies and separate populations. That is the comment, but the other interpretation, as we heard, is that lumiracoxib performed less well than naproxen, maybe because it has a risk and maybe the naproxen has some protective effect, but was comparable ibuprofen, which again raises a question whether ibuprofen has some risk attached to it. But my question is that you then said that you attributed these findings to a class effect, and since definitions are going to become very important for us going forward, I was wondering if you could tell us what you meant by a class effect and what you were referring to, is it the class of NSAIDs?

DR. VILLALBA: Yes, yes. First of all, this slide was made by the sponsor, we

didn't make the Kaplan-Meier curve, so this was just a different way of presenting the data. I don't think it was in the background package for you, and I thought it was an interesting way of looking at it, raising the issue that precisely you cannot just combine the two studies, because the sponsor also has presented the data of the two studies combined, lumiracoxib with NSAID, and you cannot just combine these two studies, because they are different studies. I agree with you, you cannot cross-compare even within the same study that had two sub-studies, so we cannot compare to other studies that were done with different designs and different entry criteria, different endpoints, so that was the point of the slide. Regarding the class effect I mentioned, I referred to the NSAID class effect. I think that if there is an effect, it is for the entire class, and that is a very heterogeneous class with different degrees of selectivity within the NSAID class. That is what I meant. Actually, let me clarify. We also thought that naproxen could be protective. I was seeing these data at the same time that I was reviewing all the other rofecoxib studies, so I guess you can understand what our position was at this time.

DR. WOOD: Dr. Furberg? No? All right. Dr. Bathon?

DR. BATHON: This was a question for Dr. Matchaba. I think there is an interesting observation about the TARGET trial. Before we even consider comparing lumiracoxib to the NSAID comparators, but just looking at the baseline APTC events in the two sub-studies of TARGET, there is an event rate of 0.43 percent in one trial and 0.84 percent in the other trial, in the

lumiracoxib-treated individuals. That is a 2-fold difference although the numbers are small. I am wondering if that could have been contributing also to the ultimate difference between lumiracoxib and the comparator drugs. Even though you used the same inclusion and exclusion criteria, could you tease out any differences in the two study populations that were enrolled into the studies that could have explained the baseline difference in events in the lumiracoxib groups? I don't mean baseline, I mean the accumulated events.

DR. MATCHABA: Thank you very much for the question. If I could have No. 8 and then could I have CV No. 67. As we discussed, the TARGET study was a combination of two studies. The only thing identical about the studies is the design of the studies, but as I mentioned in the discussion today, that this study against naproxen started about 4 to 5 months before this study against ibuprofen, and that the centers that were used for this study were different centers even within the same country, and the staggering of the recruitment was to ensure that centers were not recruiting for the same study. In some cases, countries that participated in one study did not participate in another study. Can I see the CV67, please?

We have also asked this question to say: Why are we seeing differences in the rates of cardiovascular events for the 1-1 study versus the ibuprofen sub-study? What we have done here is to look is it a center effect, and there is obviously a lot of reasons, we don't have all the answers or explanations, but if you see for the major recruiting countries, Argentina, Germany, and the U.S., that the naproxen sub-study, in terms of rates of

APTC events, were always higher than for the ibuprofen sub-study even in the same country. So, if you look at the demographic data that we also presented to you today, where 25 percent of the patients in this study were taking low-dose aspirin, where we had a difference of 14 percent versus 10 percent in high CV risk, that these populations are different in terms of baseline risk, and certainly that might be an explanation. It could be chance because the confidence intervals cross, but we don't have all the answers, but we think we have different study populations. I might ask Dr. Michael Farkouh to elaborate on that because he was involved in the design of the study and he was the primary author for the TARGET cardiovascular paper.

DR. WOOD: Have we got the question answered? I think we have. Let's move on. Dr. Abramson, did we answer your question already? Okay. Dr. Cryer.

DR. CRYER: Thank you. I have been trying to understand the differences in the results between the TARGET trial and previous outcome studies of COX-2 specific inhibitors. One very clear difference is in how the definitions were rendered. One thing that concerns me is that in the lumiracoxib experience, both your CV and GI events are defined to include people that not only had definite MIs and definite GI events, but also included those people who had probable events. Typically, I am more used to seeing trials in which we are looking at fully adjudicated definite events. When I looked here, for example, at your CV events, and eliminate what you call silent MIs and look at just what would be considered clinical MIs, there is an apparent 3-fold increase with lumiracoxib for clinical MIs compared

to NSAIDs, which dramatically differs from your other conclusion. With respect to the GI events, I think that you actually studied a low GI risk population. We know that the relative risk of COX-2 specific inhibitors to have a GI benefit is greater in a population that has low GI risk. Specifically, you didn't include anyone who had had a previous history of a GI bleed in the last year, and greater than 50 percent of your patients were less than 64 years of age. So, my question to you then is, have you re-evaluated your data using more conventionally accepted criteria, for example, fully adjudicated clinical events rather than include their probable events?

DR. MATCHABA: All the cardiovascular endpoints, APTC, including silent MI, peripheral events, deep vein thrombosis, pulmonary embolism, TIAs were all predefined and prospectively adjudicated blindly by an adjudication committee before the study started. This includes the GI or ulcer complications and PUBs with the different definitions that have been used, including clinically evident bleeds, were also predefined by a gastrointestinal committee.

DR. CRYER: I understand it may be predefined, but I am asking do you have data if you excluded the probable?

DR. MATCHABA: Yes. Perhaps Dr. Farkouh would like to comment.

DR. FARKOUH: Michael Farkouh from New York University. Our blinded adjudication committee, the definitions of probable or definite were purely on the basis of if we had all-source documentation versus our clinical

judgment of the committee, which is many years of experience. I happen to be the most junior member. A probable cardiovascular event really, in our mind, was a definite, that we just may not have had all the source documentation we needed, so it really was adjudicated as--probable was an element or a degree of definite is how I would put it.

DR. CRYER: With all due respect, I will ask the question a third time. Do you have data eliminating the subset of people who were classified as probable, and looking only specifically at those who you felt were definite events?

DR. FARKOUH: From our clinical cardiovascular committee, we did not feel there was any distinction between the two of them, so we did not mandate that. To be a probable event, I think any cardiologist that would be on this committee or anywhere else would have documented this as an event. So, it is a degree of definitiveness. We did not mandate that.

DR. MATCHABA: If I can just add to that, the answer is yes, and if you just look at confirmed cardiovascular events, the analysis is the same, and just to add, that for silent MIs besides what Dr. Farkouh has added in terms of prospective definition, there was a total of 32 clinical MIs in TARGET, and there were 8 silent MIs. Of those 8 silent MIs, 5 of them were in NSAIDs and 3 on the lumiracoxib. When we look at silent clinical MIs, we still see the same trends whether you compare the naproxen versus lumiracoxib with ibuprofen versus lumiracoxib.

DR. FARKOUH: There is a moving target here. The definition of MI has

changed over the last five to six years. We have a much more enzymatic definition of MI which we have adopted, and also the definition of silent MI has been adopted into this modified anti-platelet trial. I agree with Dr. Hennekens that it is not part of the sharp definition, but rather we were encouraged due to the signal of MI that has been seen in this class of drugs that we document silent MIs, and this was adjudicated through a blinded ECG core laboratory run at the University of Pennsylvania.

DR. WOOD: Dr. Fleming.

DR. FLEMING: Could we go to slide 33. There, I think what you have tried to do is capture the aggregation of the favorable effects on reducing upper GI ulcer complication and the unfavorable effects on the APTC. I guess my first thought is that since you didn't present the global data, I would assume the global data is your primary analysis, and by my crude calculation, the relative risk reduction is probably more towards 25 percent or so rather than the 41 percent that you are showing. But I guess more to the point, is it not apples and oranges here as you are trying to look at the aggregation of evidence? The ulcerative complication rate has been reduced from 1 percent to 0.4 percent, so we can think of it in terms of per 1,000 people, there are about 7 cases that are prevented, and the APTC is increased from 0.57 percent to 0.84 percent, so for 1,000 people, there are 3 of those cases. Isn't it a little fairer to think of it in that context? We have got per 1,000 people, 7 of these ulcerative complications prevented, and while those are substantial events, is it not true that predominantly patients recover and don't have long-term sequelae, while you are inducing 3

APTC events that are CV-strokes or MIs that have much more long-term effects? So, isn't that a fairer question, and while this picture makes it look like it is a clear positive, I would have thought the answer is much less clear, if not clearly negative.

DR. MATCHABA: Thank you. It's a fair question. If we look at this combination of safety data for the overall lumiracoxib compared to NSAIDs, the reduction in the overall population is 35 percent. It was 25 percent in the naproxen population overall, and it was not significant.

DR. FLEMING: I am focusing on just the slide you are giving, which is the slide against naproxen, so just to keep it simple in the comparison against naproxen.

DR. MATCHABA: Yes. I think the first comment we will make is that the comment was made in the VIGOR study that any events that do occur in terms of ulcer reduction and complications are negated just quantitatively by the increase in cardiovascular events. I also made the comment that this is certainly not validated, but it is an attempt on our

part that using this unvalidated method for the first time and prespecifying it and stacking up the primary endpoints, what does the picture look like relative to comparators in the same study?

DR. WOOD: What Dr. Fleming is asking you, that there is a qualitative difference--

DR. FLEMING: Apples and oranges, yes.

DR. WOOD: And a GI bleed is not the same necessarily as a stroke. They don't compensate for one another. That is not a criticism, it is just a fact.

DR. MATCHABA: Yes, that is a valid point.

DR. WOOD: And I think that is what he is saying, am I right?

DR. FLEMING: Correct.

DR. WOOD: Any other questions for the sponsors? Before anyone thinks of any, let's move along.

DR. MATCHABA: Thank you very much.