

# Committee Questions to Dr. Verburg on Celecoxib

## 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.

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### Highlights

- **RISK RATIOS:** Dr. Furberg said that Table 4 in the Pfizer briefing document showed risk ratios of 1.7 & 1.8 for thromboembolic events. Dr. Verburg responded that the rates for the composite endpoint in the meta-analysis with average duration of therapy of 1.7 months were 1.4 for placebo and 1.8 for celecoxib, a non-significant difference. Dr. Furberg said that the relative risk for “any myocardial thromboembolic events” was 1.77 in the briefing document, but that the slide presented by Dr. Verburg had “much lower relative risks”. Dr. Verburg said this was because he had used the “more meaningful endpoint and that was the APTC” but that the differences in endpoints do not “in any way change the overall conclusions”.
- **HEART FAILURE:** Dr. Furberg said that Table 6 shows a 6-fold, statistically significant increase in heart failure. Dr. Verburg said that with “hypertension and peripheral edema and heart failure” celecoxib “is associated with a significant increased incidence of all these events, as are all non-selective NSAIDs”. Dr. Furberg said ‘So, the patients didn't even have a chance to develop heart failure. You raised their blood pressure and caused fluid retention and you followed them for a few weeks.’”
- **APC TRIAL:** Dr. Wood suggested that Pfizer show a slide of the Kaplan-Meier curve from the APC trial. Dr. Verburg said that he did not have the data for that study and the APC trial would be discussed later by Dr. Hawk.
- **ADAPT TRIAL:** Dr. Cryer said that Dr. Verburg’s comment that naproxen was associated with a “significant” increase in cardiovascular risk in the ADAPT trial was “misleading”. Dr. Verburg said that this had been his interpretation of what “was put into the public domain ... but without having the data to review I can't answer that.”
- **SHORT-TERM NATURE OF DATA IN META-ANALYSIS:** Dr. D’Agostino pointed out that the short term results presented by Dr. Verburg did not exclude an increased risk that did not become apparent until 18 months of therapy. Dr. Verburg said that Pfizer had reviewed all data available to it, and that other speakers would discuss

longer term data in other indications currently being explored. Dr. Wood commented that saying that Pfizer did not have the data published in the New England Journal of Medicine “just doesn’t pass the laugh test”. Dr. Feczko (Pfizer) then said that “We are not privileged to the data. We were just given some top-line commentary about the data”.

- **CELECOXIB-INCREASED CV RISK PERSISTS IN ASPIRIN SUBSET:** Dr. Schafer said that Table 4 in the APC trial publication shows that the increased cardiovascular risk with celecoxib persists even in the low dose aspirin group. <Note: the hazard ratio in this paper was 3.8 for those taking aspirin and 2.4 for those not taking aspirin, with a p value of 0.63 between subgroups.> Rofecoxib data and Pfizer’s slide 48 appear to show similar lack of protection of low dose aspirin to the increased cardiovascular risk of COX-2 inhibitors. He therefore suggested these data “actually pretty strongly support your contention that there are other mechanisms besides the COX-1 and COX-2 balance at play here”. Dr. Verburg said that other possibilities include blood pressure-related or drug molecule-related mechanisms. Dr. Fitzgerald called this issue a “straw man” since one would expect aspirin to diminish but not abolish the risk (because thromboxane inhibition only partially reverses the effects of prostacyclin inhibition). He thought that “the in vivo basis for the molecule specific effects are tenuous to non-existent” as was the suggestion of a “pro-oxidant effect of rofecoxib”.

- **SAFETY FOR APPROVED INDICATIONS:** Dr. Gibovsky commented that drug safety concerns generated outside “the context of intended uses” may not apply to the approved indications. “Many drugs, when tested for unapproved uses, will turn out not to be safe, whereas they may very well be for the indications for which they are approved...”
- **BP EFFECTS:** Dr. Dworkin asked about BP effects of celecoxib 200 mg BID. Dr. Verburg said there were “very minor differences” compared to placebo. Dr. Friedman asked about BP effects of celecoxib in longer term studies in larger numbers of people. Dr. Verburg asked Dr. Welton, a Pfizer consultant, to comment. Dr. Welton said that NSAIDs increase BP on average by 5 mmHg and that this effect is primarily seen in patients on antihypertensive therapy, raising the question of a drug-drug interaction. The celecoxib database showed “that there really isn't much in the way of hypertension adverse events reported” but with rofecoxib there was a “very obvious dose-correlated increase in hypertension events”. To resolve this he and his colleagues did a double blind ambulatory BP comparison of celecoxib and rofecoxib in patients receiving antihypertensive drug therapy. This trial showed that rofecoxib but not celecoxib showed “early disruption of blood pressure”. Other studies have shown that BP changes of even 2 mmHg are associated with differences in mortality. <See slides at end of this document for BP data shown by Dr. Welton> Later, Dr. Nissen commented that, since

celecoxib has a shorter half life than rofecoxib, “the effect of the drug may be gone toward the end of the dosing interval, which would tend to bias the study in favor of celecoxib”.

- **COMBINED ANALYSIS OF SEVERAL NIH STUDIES:** Dr. Furberg commented that information on cardiovascular outcomes was supposed to have been collected from a number of NIH studies with celecoxib and he was concerned that “the NIH has dropped the ball”. “So, I think we should request that information and, if necessary, even go to the director.”
- **SHOULD FOCUS ON PLACEBO-CONTROLLED STUDIES:** Dr. Furberg said that the focus should be on placebo-controlled rather than active-controlled trials.
- **FOCUS ON LONG-TERM STUDIES:** Dr. Fleming suggested the focus should be on “on the half a dozen studies that have longer-term follow-up “. If one groups “atrial SAEs, anginal SAEs, MI and thrombophlebitis” in non-aspirin users in the CLASS trial, there were “four times as many events on Celebrex than ibuprofen”. The APC trial shows “a three-fold increase in the rate of CV death, MI and stroke” versus placebo. The 97-02-001 trial “had I think a doubling in the rate of targeted events”. “The PreSAP and the ADAPT trials will also be very informative.” Dr. Verburg said that the Pre-SAP results were to be reviewed in the afternoon by Dr. Levin and that he (Dr. Verburg) had no non-public information about the ADAPT trial. Dr Verburg said that the 97-02-001 trial was difficult to interpret because of small numbers

and a lack of stratification by risk factors. However, “we didn’t entirely dismiss it” and performed a “blinded adjudication process” of all serious cardiovascular events.

- **CELECOXIB VS. NSAID+PPI:** Dr Shafer asked if there were data comparing celecoxib alone with a combination of a non-selective NSAID with a proton pump inhibitor. Dr Verburg said he was not aware of any data “with respect to whether patients stay on therapy longer with celecoxib alone versus the combination of an NSAID and, say, a proton pump inhibitor”.
- **CELECOXIB/ROFECOXIB EQUIVALENT DOSES FOR BP, EFFICACY AND COX-2 INHIBITION:** Dr. Nissen said that “I have certainly heard is that the equivalent dose of celecoxib to 25 mg of rofecoxib is 200 mg BID, not once a day. “ He asked if there were data comparing efficacy and BP effects of celecoxib 200 mg daily and rofecoxib 25 mg daily. Dr White (Pfizer consultant) responded that he did 2 controlled studies. One ambulatory BP study of celecoxib 200 mg bid and placebo in patients on ACE inhibitors showed no statistically significant difference with a mean systolic BP difference of 1.3 mmHg. With regard to efficacy, a 500-patient, 12-week controlled OA study in hypertensive diabetics receiving an “angiotensin blocker” compared the effects of celecoxib 200 mg daily, rofecoxib 25 mg daily and naproxen 500 mg BID showed equivalent efficacy whereas rofecoxib alone showed an increase in blood pressure (4.2 mmHg). At the end of this discussion, Dr. Braunstein asked to show a slide of

the rofecoxib and celecoxib dose-response curves for 24-hour COX-2 inhibition (as measured by ex vivo PGE-2 inhibition). This showed equivalence of rofecoxib 25 mg/day with celecoxib 200 mg BID, and equivalence of rofecoxib 12.5

mg/day with celecoxib 200 mg once/day. Another clinical study showed equivalent efficacy (as measured by Patient Global Assessment) between rofecoxib 12.5 mg/day and celecoxib 200 mg once daily.

## Discussion Text

DR. WOOD: Thanks very much. Questions from the committee? Yes?

DR. DWORKIN: Could you go back to the blood pressure slide, and do you have any data on what it would look like if you had 400 mg daily of celecoxib? I think you just showed 200 mg. I am sort of interested in 200 BID.

DR. VERBURG: We do not have a direct comparison of 200 mg BID celecoxib versus rofecoxib. We have done a 24-hour ambulatory blood pressure trial evaluating 200 mg BID of celecoxib relative to placebo, and we have found very minor differences in the blood pressure profile of celecoxib at that dose as compared to placebo. That is as close as I can come to that.

DR. WOOD: Curt?

DR. FURBERG: I think the focus of your presentation troubles me a bit. You really spent most of the time on comparative trials, and if you are really interested in safety comparing two active drugs is not the best way to go. You get much better information by looking at the placebo-controlled trials. I think we are here to answer two questions, is Celebrex safe? And I think what you

talked about is not going to help us answer that question. We need to look at the placebo-controlled trials. You answered the second question, is the safety of Celebrex different from the NSAIDs? Let's come back to the placebo-controlled trials. There is information in the briefing document from Pfizer that you did not bring out, and I would like to refer people to table 4 which presents a summary on the Celebrex experience in placebo-controlled trials, and it is showing risk ratios of 1.7, 1.8 versus placebo for thromboembolic events—trends that are not too dissimilar to what we see in other placebo-controlled trials of the other COX-2s. I think in addition to that, you did not address at all the issue of heart failure that we talked about earlier. We were informed that in the APPROVe study there was a 4-fold increase in heart failure in that placebo-controlled trial. For Celebrex, if anything, it is worse. If you look at your table 6, although there are small numbers, there is a 6-fold increase in heart failure, statistically significant, and that is not mentioned. So, if you are going to talk about safety, my plea is that let's look at all aspects of safety, including the thromboembolic events and heart failure, and let's pay a little bit more attention to the placebo-

controlled trials because, as has been said over and over again, we really don't know the safety profile of the various non-selective NSAIDs, and to compare to those drugs is not very informative. Thanks.

DR. WOOD: Do you want to respond to that?

DR. VERBURG: I think the only way to respond to that is actually review some of the data. Why don't we take a look at a couple of the slides? Huh? So, why don't we go to slides C-112? Going back to the meta-analysis, with the caveats that it is 11,000 patients and it is 6 weeks of exposure and it is roughly 31 events. So, we are shaping conclusions based on a very small dataset over very small durations. The composite endpoint for placebo was 1.4 in terms of events per 100 patient-years as compared to 1.8 for celecoxib. In terms of cardiovascular death and MI, you can see that the results were lower with placebo and there was no difference in non-fatal stroke. Indeed, if you plot these out in terms of relative risk, you find that the point estimate of relative risk for three of these endpoints favors placebo but the confidence intervals are fairly substantial, indicating very low precision around those points.

DR. WOOD: What was the exposure for that?

DR. VERBURG: Six weeks.

DR. WOOD: I think we should emphasize that. You missed that out. Just go back to the slide.

DR. VERBURG: This is 1.7 months of exposure.

DR. WOOD: As long as we have that on the record.

DR. FLEMING: But in essence, if you are doing a non-inferiority, if you want to show you are not worse, there is a major issue of you are not giving very long exposure here as to whether you might be really underestimating excess risk.

DR. VERBURG: In our view, that is why we did not focus on these data in the presentation. We felt it was really non-informative and we would really leave the discussion of placebo comparisons over longer term to Dr. Hawk and Dr. Levin when they present.

DR. WOOD: Well, why don't we put up the Kaplan-Meier curve from the trial, the APC trial?

DR. VERBURG: Again, I don't have those data.

DR. FURBERG: For any myocardial thromboembolic events the relative risk is 1.77. So, I don't know why you have that discrepancy. You have much lower relative risks in your slide than in the briefing document that was sent to the committee members.

DR. VERBURG: I probably should step back, it is a little bit different construct in my presentation than in the briefing book, and it was really based on our desire to get to what was a more meaningful endpoint and that was the APTC. I don't think that the differences between the analyses in any way change the overall conclusions.

DR. FURBERG: Well, we may disagree on that point. How about heart failure then?

DR. VERBURG: Sure. Let me just check my notes here. Can you bring up for me C-248? These are data that were provided in the briefing book I believe--  
DR FURBERG: Correct.

DR. VERBURG: --comparing celecoxib to placebo in terms of reports of adverse events from investigators, not adjudicate, hypertension and peripheral edema and cardiac failure, and celecoxib is associated with a significant increased incidence of all these events, as are all non-selective NSAIDs. Let's go to the next slide.

DR. WOOD: What duration?

DR. VERBURG: Same duration.

DR. WOOD: Six weeks treatment?

DR. VERBURG: A mean of six weeks of treatment.

DR. FURBERG: So, the patients didn't even have a chance to develop heart failure. You raised their blood pressure and caused fluid retention and you followed them for a few weeks. They didn't have a chance to get into heart failure.

DR. VERBURG: So, let's step back. What we are doing is we are trying to determine some cardiovascular safety parameters from trials that were designed to test fundamentally the efficacy of arthritis.

DR. FURBERG: Sure.

DR. VERBURG: So, again, we have recognized all of the faults in what we are doing. There is no getting around that. But if we want to see what the data look like in order to form some conclusions, this is what it looks like. We hear the criticism but, again, these are from NDA trial databases of 12-week, placebo-controlled trials to evaluate efficacy in arthritis. So, we are limited by the purpose of those trials.

DR. FURBERG: Yes, but these are trials that you designed and set up, and you are not providing the answers that we need to evaluate the efficacy and safety.

DR. WOOD: I don't understand the answer to the last question. You are telling us you don't have the data that you published in The New England Journal two days ago with you in this presentation of a placebo-controlled trial?

DR. VERBURG: I do not. That trial was conducted by the National Cancer Institute.

DR. WOOD: You are welcome to download a slide from The New England Journal. They have a web site that let's you do that.

DR. VERBURG: And we will cover that topic later. I just don't have a slide with that in my presentation.

DR. WOOD: Any other questions?  
Byron?

DR. CRYER: Yes, throughout your presentation you suggested that there may be cardiovascular risk, specifically thrombotic risk associated with non-selective NSAIDs. You suggested this

mechanistically with ibuprofen and with naproxen based upon the ADAPT trials from observations. My sense and my understanding of the literature is that there are no good data with non-selective NSAIDs to suggest an increased cardiovascular risk when one looks at meta-analyses, specifically a meta-analysis published by Garcia Rodriguez as recently as 2004. The relative risk of ibuprofen was right at 1 and there was a relative risk for an overall reduction of events, albeit modest, associated with naproxen. My specific question to you is that in the ADAPT trial you stated that the increase in events with naproxen was significant. My question is do we, in fact, know whether that increase was statistically significant because my assessment of the math from the ADAPT trial, given the limited data that we have, is that it is mathematically unlikely that the increase in events with naproxen would be statistically significantly increased.

DR. VERBURG: We have not seen the data so I think it is speculation. My interpretation of what was put into the public domain is that there were significant differences, but without having the data to review I can't answer that.

DR. CRYER: But I think your wording is very important and somewhat misleading because you specifically say "significant" and many of us, when we hear the word significant, we are led to a conclusion that that is a statistically significant increase. And without having the data, as you just said, I think it is just a little misleading. All we can say for now is that there was a numerical increase which, if not statistically

significant with naproxen, could have been entirely due to chance.

DR. VERBURG: Point taken. Thank you.

DR. WOOD: Ralph?

DR. D'AGOSTINO: I just want to get clarification from you. Given the discussion we had previously with the APPROVe trial and waiting 18 months before you started seeing a separation of serious events, and so forth, how do you respond? I mean, your presentation was talking about six weeks, a year at most. So, how do I interpret your presentation? And I was going to ask about the placebo trials also.

DR. VERBURG: So, the purpose of my presentation really was to go back and review what we know about the cardiovascular safety of celecoxib in the approved indications for this drug, which are osteoarthritis and rheumatoid arthritis. We reviewed all of the data that is available to review the safety of that drug versus placebo or versus alternative therapies. Subsequent speakers I think will expand into other indications that are currently being explored.

DR. D'AGOSTINO: So, your presentation would leave it that we really don't know what to make out of any long-term use?

DR. WOOD: Wait a minute. It is one thing to say you presented the data for placebo-controlled trials in the approved indications, but it is not reasonable to say you presented all the data in placebo-controlled trials. The largest placebo-controlled trial presented in The New England Journal you haven't

presented and you say you don't have the data here. That just doesn't pass the laugh test. Here it is, do you want it?

DR. VERBURG: I have seen it.

DR. FECZKO: Just for clarification of this, the APC trial will be presented I think later on this afternoon by Dr. Hawk. It is sponsored by the National Cancer Institute. We were not part of that trial. We are not privileged to the data. We were just given some top-line commentary about the data. The same holds for the ADAPT trial. We were not part of that data safety monitoring board or the results of that trial. I believe that is planned to be presented on Friday.

DR. D'AGOSTINO: My concern is the conclusions which we heard. I mean, you know something is coming down the line and why were these conclusions given as opposed to saying here is what we have at this point in time and walking away from it? It is a very positive presentation.

DR. WOOD: Dr. Manzi?

DR. MANZI: I think probably my questions can wait until they review the APC trial because it really has to do with the long-term issues.

DR. WOOD: All right, thanks. Dr. Shafer?

DR. SHAFER: One might think I am fixated on low dose aspirin here, and perhaps I am. But once again we have three bits of information on low dose aspirin. We have table 4 in the handout that Pfizer prepared or the document that Pfizer prepared which again shows that actually the risk factors that existed, in

fact, got worse on low dose aspirin. We have in the APC trial, which will be coming up, table 4 from those data, again showing that the risk factors maybe were ameliorated a little bit but still with low dose aspirin the risks persisted. So, we don't have a protection, if you will, from low dose aspirin. Then in your own slide 48, now in 48 it is not a placebo-controlled result and it is not blinded, but we can use the relative risks in the ASA versus non-ASA used for the other drugs to see that in the case of the high-dose rofecoxib group low dose aspirin conferred no protection. Do these data, this sort of persistent signal that low dose aspirin provides no protection--are those data that actually pretty strongly support your contention that there are other mechanisms besides the COX-1 and COX-2 balance at play here?

DR. VERBURG: I am not sure that I follow where you are taking the question.

DR. SHAFER: You had suggested that perhaps there is something else besides the COX-1-COX-2 balance.

DR. VERBURG: Right.

DR. SHAFER: If it is the COX-1-COX-2 balance low dose aspirin ought to make these COX-2 drugs look like non-selective drugs.

DR. VERBURG: Correct.

DR. SHAFER: The fact that low dose aspirin doesn't do that repeatedly would look to me to support your contention that there is something else going on, and that is what I am asking. Is this something that Pfizer has considered? Have you had more thoughts on that?

DR. VERBURG: Only to reiterate some of the thoughts that I think were brought up this morning, and that is that this would not necessarily obviate or alter any changes in blood pressure that might occur with these drugs. It might but it might not. Also, it sort of lends itself to is there other molecule-based pharmacology that could moderate or modulate the effects that one sees from one compound to another? But that is about the extent of it.

DR. WOOD: Garret, this keeps coming up. Do you want to address this?

DR. FITZGERALD: It is always difficult to address a straw-man when the construct is laid out and the arguments are assembled. I find the aspirin story really straws in the wind as opposed to anything definitive. For example, a comment was tossed out about blood pressure. We have absolutely no information as to whether low dose aspirin impacts on the blood pressure elevation by COX-2 inhibitors by controlled experience. I think as far as the mechanistic issues that we talked about this morning, we would only expect aspirin to have a diminishable effect as opposed to an abolitional effect on that type of hazard because, as I mentioned this morning, it isn't a prostacyclin-thromboxane Ying-Yang balance. Prostacyclin acts as a more general constraint on factors that transmit cardiovascular risk. So, I find the arguments unpersuasive. As far as molecule specific effects are concerned, it is quite true that almost every drug has multiple mechanisms of action that relate to dose-response relationships. But, in contrast to the mechanism we discussed this morning, the in vivo basis

for the molecule specific effects are tenuous to non-existent and that includes the pro-oxidant effect of rofecoxib which is based on one paper in the literature using quantitative estimates of oxidative stress that those of us in the community view as highly questionable. Thank you.

DR. WOOD: I think your job, Garret, is to take Dr. Shafer for a drink and make sure that the two of you have sorted this out tonight! Dr. Domanski?

DR. DOMANSKI: I was just waiting for discussion of APC and I can wait a bit longer.

DR. WOOD: All right. Dr. Dworkin?

DR. DWORKIN: Yes, given the results that you allude to for the APC trial, suggesting that you don't really begin to see a difference until after a year, do you think it is going to be ethically possible, going forward, to do long-term placebo-controlled trials of celecoxib? You were suggesting that we need to do that, but I am not sure how given the results that we have in The New England Journal.

DR. VERBURG: I don't really want to address the question of ethics. I think I will step back and answer the question as follows: The APC was not the only trial which you will hear today. There is also another trial that shows that there was no risk associated with celecoxib. What does that inform us about the true risk of celecoxib over the long run? Relative to placebo, the drug may carry a cardiovascular risk. That I don't think is something that is known entirely. If the risk is there it seems to be small because it is not seen on a consistent basis. You could throw in the ADAPT trial. The

results there are shown to be the same. So, our sense is that you know something about the long-term cardiovascular profile of celecoxib. You know nothing about the long-term cardiovascular effects perhaps of non-steroidals. Yet, many patients would take them continuously. So, I don't know that it necessarily would be unethical. In fact, you might suggest that it would be mandatory for us to go and evaluate that. Patients have a need and a desire to know what risks they will be taking with their drug, not just in comparison to alternative therapies but what is the true risk if they decided not to select any therapy at all.

DR. WOOD: Allan?

DR. GIBOFSKY: Just a comment. I think it is important when we consider the safety issue to bifurcate the safety issue because there may be a dichotomy between how we are approaching it. I think some are approaching it with is the drug safe, while others are approaching it with is the drug safe for the intended use as prescribed in the label? I think those are two very different issues. The test of whether a drug is safe or not, to test it across all indications is one thing. To test it across all other indications is something else. So, I really think we need to discuss safety in the context of intended uses. Many drugs, when tested for unapproved uses, will turn out not to be safe, whereas they may very well be for the indications for which they are approved, and that is why I think we have to be a bit relative in our discussion as well as being absolute.

DR. WOOD: Dr. Friedman?

DR. FRIEDMAN: Two points, first, you touched briefly on the issue of blood pressure. Surely, there must be ways of getting some good data on what celecoxib really does to blood pressure. The data you have shown are from relatively small numbers of people, followed for a very short time, and we don't know anything at all about what other medications or how they were otherwise protected. Do you have any plans for getting better, longer-term information in a more consistent way?

DR. VERBURG: Well, I think what I would like to do is turn the discussion over to Dr. Welton who has been studying the blood pressure effects of celecoxib and NSAIDs for many years. He can at least recapsulize for you what we have and perhaps also indicate what the future directions might be.

DR. WELTON: Thank you so much. Andrew Welton, from Baltimore. I have, I have to tell you quite frankly, been itching to get up here to the microphone to clarify at least the clinical aspects of the evolution of the blood pressure story because I do not think it has come across entirely clearly either this morning or this afternoon, specifically, the human component thereof. So if you will bear with me for a moment, I will tell you, if I might have slide C2-42, that sequence, please? I would point out that this is a fascinating story that first came to our attention with NSAIDs in 1993. These were the observations of Janet Pope, who was then a first-year rheumatology fellow, who pointed out in this meta-analysis, published in *The Archives of Internal Medicine*, that, indeed, all NSAIDs, when compared with placebo, do distort blood pressure and elevate blood pressure. If I might have the next

slide, the following year we learned something else in an additional meta-analysis. That was, once again, that NSAIDs disrupt blood pressure, the mean increase being 5 mm, but particularly learned that this dominantly emerges during the treatment of hypertension, which then set up the issue that maybe we are looking at an issue of drug-drug interaction. If I might have the next slide, this was about the time frame with respect to the start of the first two coxib development programs and, therefore, we were very mindful of the importance of blood pressure as these drugs went into a human evaluation. I show you here the data for the osteoarthritis studies as they were incorporated into the new drug application. You can see, scanning from left to right, that there really isn't much in the way of hypertension adverse events reported, and here we are at the mercy of the investigators doing the trials. In the CLASS trial, as

Dr. Verburg already pointed out, additionally not much in the way of blood pressure. If I might have the next slide, taking exactly the same approach, using NDA osteoarthritis trials for the second of the coxibs, this then gave us the emergence of a very obvious dose-correlated increase in hypertension events but, again, at the mercy of the investigators doing the trials. This wasn't correlated with specific elevations in blood pressure. Next one, please. It was at this point that I and my colleagues thought the only way to resolve this correctly is to do head-to-head, prospective, double-blind, randomized trials. And, the logical subset in which to do these studies is, in fact, patients who are being treated for hypertension because this was emerging now more as

a story of disruption of blood pressure control rather than the genesis of new onset hypertension. In brief, our first trial was powered to look for a 3 mm or greater difference in blood pressure effects between the two coxibs using that because it is a guidance rule from our colleagues in the Cardiorenal Division of the FDA. The essence of it is it showed in treated hypertensives early disruption of blood pressure with rofecoxib, as seen on your left; continued for 6 weeks of observation; and not seen with celecoxib. This was reasonably curious. Standard rule of thumb, make sure your observations are correct. So, on the right-hand side of the panel it shows repeating these studies in over 1000 people. Next one please. The additional issue that emerged--

DR. WOOD: Try and get to the point quickly because you are answering a single question and we are running really short of time.

DR. WELTON: I understand. Mr. Chairman, I beg your pardon. Bear with me for a moment.

DR. WOOD: One moment.

DR. WELTON: Over 24 hours pressures are sustained. Next one. There are differences in the antihypertensive drugs. There are differences seen in the responses of the drugs also at the doses that cause comparable efficacy. Next one, please. Let me simply wind up. If I might have the next one, please. As you will see at the top right-hand side, what it shows is that if you shift in the population blood pressure by as little as 2 mm, on the right-hand side at the bottom, you can see the reduction in mortality. So, these small changes in

blood pressure in large numbers of patients are very, very important. I would end to answer the question of Dr. Nissen that he asked earlier on, if I might have C-28-3, and that, Mr. Chairman, is my final point.

DR. WOOD: It really is. <Laughter>

DR. WELTON: Here we are showing elevations of greater than 20 mm Hg and it does show between these two coxibs there are important differences in these big swings in blood pressure. I regret I cannot show you placebo results in this trial because we didn't incorporate them but that speaks to your earlier question, Dr. Nissen.

DR. WOOD: Thanks a lot. Curt?

DR. FURBERG: I just wanted to say for the record that we have some missing information. There is a fairly large number of studies sponsored by the NIH that have information on cardiovascular outcomes. An effort was initiated to get that information together but no real follow-up. So, it looks to me like the NIH has dropped the ball and not provided the information that we need from those other trials.

DR. WOOD: Cardiovascular outcomes in what? In celecoxib?

DR. FURBERG: Yes, with Celebrex, yes.

DR. WOOD: I see.

DR. FURBERG: So, I think we should request that information and, if necessary, even go to the director.

DR. WOOD: Tom?

DR. FLEMING: I commented earlier about how one struggles to try to interpret the data when there are such short-term interventions, the 41 trial meta-analysis that if you focus on the placebo control you only have 6 weeks of treatment. It certainly tempts me to focus much more on the half a dozen studies that have longer-term follow-up. You mention in slide 36, the CAESAR trial and the CLASS trial, although diclofenac is the control and, as Dr. FitzGerald said, is that Celebrex with hepatic side effects? What does it mean if there is not a difference? Interestingly though, when you look at the CLASS trial and the non-aspirin users there is also an ibuprofen arm and the summary that is given here is in atrial SAEs, anginal SAEs, MI and thrombophlebitis. There are four times as many events on Celebrex than ibuprofen in the non-ASA users. If we go to the placebo-controlled trials, we have seen that in the APC trial there is a three-fold increase in the rate of CV death, MI and stroke. Another placebo-controlled trial that you didn't mention is the Alzheimer's trial, the 97-02-001 trial, that being placebo-controlled is of interest, and it had I think a doubling in the rate of targeted events. Then, the last issue related to this is the PreSAP and the ADAPT trials will also be very informative, and I am very confused in exactly what you do know. I think someone has already alluded to. On slide 821 it is written as though you know that these results will be neutral or favorable. So, I have a multi-component question here, am I interpreting this--can you tell us more about the Alzheimer's 97-02-001 trial? And, what exactly do you know today about the PreSAP and ADAPT trials?

DR. VERBURG: Let me start with the second one first. So, the PreSAP results will be reviewed by Dr. Bernard Levin later this afternoon in full detail. So, those results will be disclosed to the committee. For the ADAPT trial I know no more than what has been published, what has appeared in the newspapers, nothing more.

DR. FLEMING: And what about the 97-02-001 trial?

DR. VERBURG: Right. So, let's go to slide C-214. Let's talk about this for a minute. So, the Alzheimer's trial, study 001, was a small randomized trial comparing celecoxib 200 mg twice daily to placebo over one year of treatment. Notice that the randomization was 2:1 and that the mean patient exposure was on the order of about 10 months or so. This goes back now to the concept that we used in the briefing book and we will update this in a minute, but for any cardiovascular event you can see that there were 3 events versus 11 events. There were 4 myocardial events in total. Two of those I believe were angina and 2 were MI. Cerebrovascular events are listed here and then further down. Of course, these are based on investigator reports to us. Also, if we go back--

DR. FLEMING: Well, before you leave this slide, which I guess you have just done--is there data that you have on heart failure as well?

DR. VERBURG: I am sure we do. I just don't have that right at hand but we can certainly get that for you. I just don't have that in my presentation. I am looking for the background medical history in this trial. Do I have the wrong slide number? So, what concerned us a

little bit about the results of the trial you can see here, again coming back to my comment earlier, when the purposes of the trial are not cardiovascular in nature, they can be heavily confounded because you are not controlling for distribution of patients by risk factor. So, what you see here is a trend for a higher degree of underlying risk in this patient population. Also, I want to add one comment--

DR. FLEMING: Although somewhat modest I would say when you are looking at relative risks of 2 in the outcomes. A valid point, small numbers, but it doesn't explain a large part.

DR. VERBURG: So, we didn't entirely dismiss it there either so we took it one step further and, in fact, at about the time of the CLASS and the VIGOR results we did employ a blinded adjudication process of all cardiovascular events, serious cardiovascular events that Dr. William White, who is with us today, conducted along with some of his colleagues. That trial was published several years ago. Could I have slide C-217? That article that Dr. White wrote was targeted to arthritis patients. At the time, he and his co-workers also adjudicated the events from the Alzheimer's trial. Dr. White, if you would care to make a comment? I think you are most informed on these results.

DR. WHITE: Thank you. William White, University of Connecticut Cardiology Center. So, these were done in accordance with the other clinical trials that you have heard, using strict criteria between two blinded adjudicators. As you can see, there was a 2.9 percent incident rate in the placebo group and a 3.5 percent rate in the

celecoxib group, which was not statistically different. To answer the heart failure question, there were just too few cases of adjudicated heart failure, not different between the two treatment groups.

DR. WOOD: So, these were adjudicated events that had already been reported? Or, were these prospectively defined?

DR. WHITE: Yes.

DR. WOOD: So, tell us what you did.

DR. WHITE: I am not sure what you are asking, were the cases prospectively defined when the study started?

DR. WOOD: Right.

DR. WHITE: No.

DR. WOOD: So, maybe somebody should comment on that. Richard, to you want to comment? Okay, well, we will get to that.

DR. FLEMING: For heart failure you said there were two adjudicated cases. They broke out in what manner?

DR. WHITE: I believe it was equal in each group. It was a very small number. There was either one and one or two and two. I can't recall, to tell you the truth.

DR. FLEMING: Why don't we check?

DR. WHITE: We will check.

DR. WOOD: Any other questions? Dr. Shafer?

DR. SHAFER: This does not involve aspirin.

DR. WOOD: Thank goodness!

DR. SHAFER: One of the things we are looking at is overall safety, and you brought up the subject about alternatives, NSAIDs being the alternative. What data are there about celecoxib GI tolerability versus NSAIDs when combined with a proton pump inhibitor?

DR. VERBURG: I am not aware of any data that evaluate GI tolerability issues--

DR. WOOD: There is lots of data on that.

DR. VERBURG: There are data with respect to complicated ulcers, but with respect to whether patients stay on therapy longer with celecoxib alone versus the combination of an NSAID and, say, a proton pump inhibitor, I am not aware of any such data.

DR. WOOD: Do you want to take that, Steve? No? Actually, the last sponsor presented some of that data in their presentation.

DR. NISSEN: I want to explore with you for a moment the issue--you have several times used the term "equally effective doses" and this is important. In several of the trials we see a relationship between dose and the amount of cardiovascular toxicity. It is particularly important because you have done a lot of blood pressure comparisons between rofecoxib and celecoxib and one of the arguments I have certainly heard is that the equivalent dose of celecoxib to 25 mg of rofecoxib is 200 mg BID, not once a day. So, I would be very interested in understanding that, particularly when you consider that there

is a much shorter half-life and, you know, particularly if you do an ambulatory blood pressure study the effect of the drug may be gone toward the end of the dosing interval, which would tend to bias the study in favor of celecoxib. So, could you address any data that you have that indicates that 200 mg once a day has the same effectiveness as 25 mg of rofecoxib?

DR. VERBURG: 200 mg of celecoxib in terms of 25 mg of rofecoxib in terms of effectiveness?

DR. NISSEN: Yes, I want to know about efficacy, and then I would also like to know about any blood pressure comparisons of 200 BID to 25. I am trying to understand. You have made a case that the drugs have a very different effect on blood pressure and I am testing that a little bit with you to make sure that we got that right.

DR. WHITE: Do you want me to answer that?

DR. VERBURG: Yes.

DR. WHITE: Well, I have conducted two controlled clinical trials in this regard. The first one was done about three or four years ago in 178 patients treated with celecoxib at 200 mg twice daily versus placebo twice daily, specifically in hypertensives treated with an ACE inhibitor to bring out the worst-case scenario with regard to interference with the drug. The 24-hour systolic blood pressure difference was 1.3 mm Hg between celecoxib at 400 daily and placebo, which was not statistically different. That was giving it BID. Now, in the other realm, not placebo controlled but published two weeks ago

in The Archives of Internal Medicine, was a 500-patient study in which patients with osteoarthritis of the hip or knee, plus hypertension, plus type II diabetes, also treated with a angiotensin blocker were then randomized to celecoxib 200 daily, rofecoxib 25 daily and naproxen 500 BID. At 6 and 12 weeks into the double-blind period a very formal cluster of arthritis efficacy assessments were made using the same standards for any arthritis drug, and they were, in fact quite equivalent using WOMAC and Visual Analog Pain Score and so forth. So, from the patient perspective at 6 and 12 weeks, they were therapeutically equivalent. At those same endpoints as you already saw, there was a significant pharmacodynamic interaction between rofecoxib and perhaps the underlying treatment because there was very little salt and water retention, evident based on edema and weight gain, with about a 4.2 mm increase in 24-hour systolic pressure. That was a sustained increase during the daytime. With regards to naproxen and celecoxib, there was no such increase seen, yet, there was clinical equivalence with the regards to anti-inflammatory responses. That is pretty much what there is. There are no other studies like those.

DR. VERBURG: Dr. Simon, do you have a comment?

DR. SIMON: Yes, I was one of the authors of the hypertension study in the Archives. As a hypertension study and as a rheumatologist, why would I be involved in such a study? In fact, I was involved to ensure that the outcome measures for osteoarthritis, as measured by Patient Global and WOMAC, which is a functional outcome scale, and the VS

scale for pain would then be the appropriate way to look at equivalence of benefit. The data sets that suggest that there isn't equivalence in this kind of analysis of 200 mg versus 25 are really based on different ways to look at the evidence, such as night pain and other aspects of components of some of these outcomes. This was really a very robust way that is, in fact, typically used for approval at the FDA in determining efficacy of a particular therapeutic. And, we were able to demonstrate both at 6 weeks and at 12 weeks that there were equivalent benefits. But you are absolutely correct, differences in half-life, if you ask different questions will give you different responses.

DR. WOOD: Do you really want to say something because I really want to get to the next--all right.

DR. BRAUNSTEIN: Yes, I just want to show—

DR. WOOD: Be quick.

DR. BRAUNSTEIN: Well, I will show you actually the pharmacologic responses for COX-2 inhibition.

DR. WOOD: All right, go ahead.

DR. BRAUNSTEIN: This shows you the average 24-hour inhibition of COX-2 for different doses of rofecoxib and celecoxib. This is a standard ex vivo PGE-2 inhibition assay. What you can see is that there is a dose response, as we know, for all NSAIDs to inhibit COX-2, and over 24 hours celecoxib 200 mg twice a day has the equivalent COX-2 inhibition of approximately rofecoxib 25 and celecoxib 200 once a day is roughly the same as rofecoxib 12.5. May I have

233? These are the results of a clinical study looking at Patient Global Assessment in response to therapy, acetaminophen 4000, celecoxib, rofecoxib 12.5 and then rofecoxib 25. Without getting into an argument--although statistically rofecoxib 25 had the greatest effect, you can see that rofecoxib 12.5 is the dose that has the most similar efficacy to celecoxib 200 once a day, you know, similar to what you would expect based upon the pharmacologic and the pharmacodynamics.

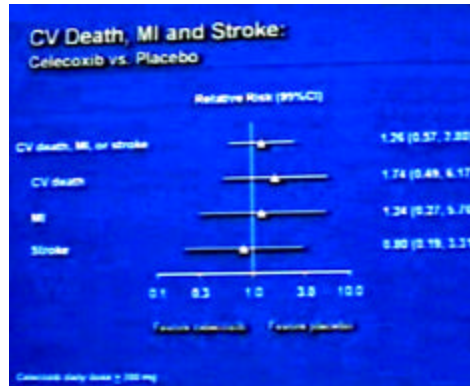
# Slides shown during Discussion

Note: Some of the slides presented may not be included below.



### CV Death, MI, Stroke: Celecoxib vs. Placebo

	Placebo	Celecoxib 200 mg
N	4057	4057
Patient-years	585	728
Mean exposure/patient (mo)	1.7	2.0
CV death, MI, stroke	8 (1.4)	23 (3.1)
CV death	3 (0.5)	11 (1.5)
MI	2 (0.3)	7 (0.9)
Stroke	3 (0.5)	5 (0.7)

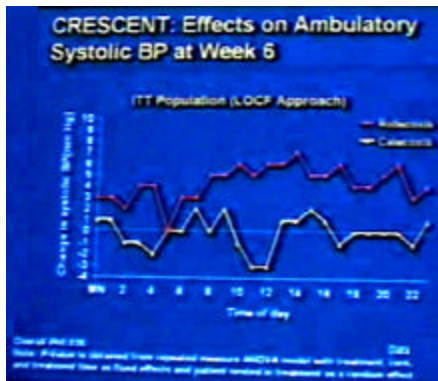
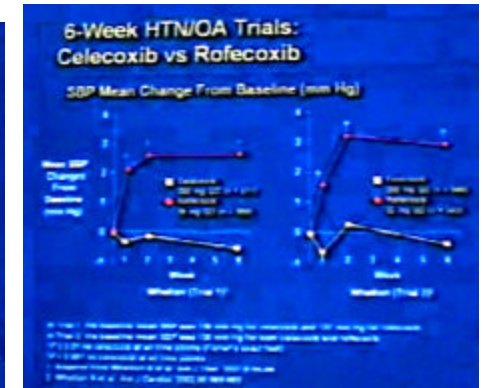
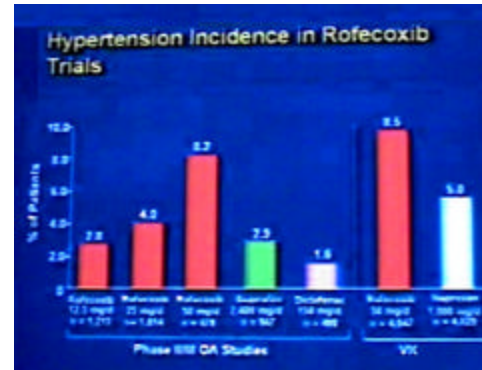
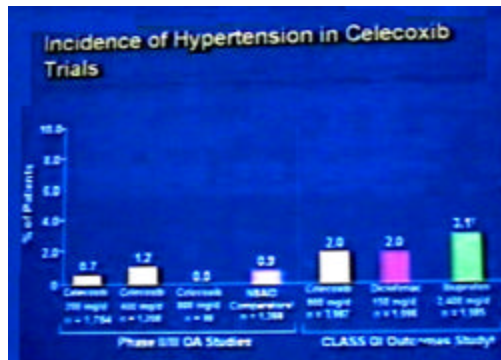


### Incidence of Cardiorenal Events: Combined Analysis of RCTs

	Placebo	Celecoxib 200 mg daily	P-value
N	4057	4057	
Hypertension	27 (0.7)	91 (1.1)	0.023
Peripheral edema	25 (0.6)	171 (2.0)	<0.001
Cardiac failure	1 (<0.1)	13 (0.2)	0.046

### NSAIDs - Blood Pressure Meta-analysis (Johnson, Nguyen, Day; Ann Int Med 1994)

- 771 patients, mean age 47.6 yrs with male:female ratio of 1.3:1
- Mean increase in supine BP of 5.0 mmHg (CI 1.2 to 9.6 mmHg) for NSAIDs pooled
- Hypertensive patients: mean increase in supine BP was 5.4 mmHg (CI 1.2 to 9.6 mmHg)
- Normotensive individuals manifested approximately 1 mmHg BP elevation
- Among NSAIDs, piroxicam produced the most marked elevation in BP (6.2 mmHg) followed by indomethacin (5.7 mmHg); sulindac and aspirin had the least effect on BP



### Thromboembolic CV Events: Alzheimer's Disease Study 001

	Placebo	Celecoxib 200 mg bid
N	140	295
Patient-years	120	250
Mean exposure/patient (mo)	10.3	10.8
Any CV Event	3 (2.1)	11 (3.9)
Myocardial	0 (0.0)	4 (1.4)
MI	0 (0.0)	2 (0.7)
Cardiovascular	3 (2.1)	7 (2.5)
Stroke	2 (1.4)	6 (2.1)
Peripheral vascular	0 (0.0)	4 (1.4)

### Alzheimer's Disease Study 001: CV-Related Medical History

Medical History Term	Placebo	Celecoxib 200 mg bid
N	140	295
Hypertension	31 (22.1%)	91 (21.9%)
Diabetes	10 (7.1%)	28 (8.3%)
CABG	1 (0.7%)	9 (2.2%)
Stroke/TIA	4 (2.9%)	15 (3.3%)
Coronary artery disease	1 (0.7%)	8 (2.3%)

### Alzheimer's Disease Study 001: Unadjusted Incidence Rates Primary CV Events\* from Independent Adjudication

	Placebo	Celecoxib 200 mg bid
N	140	295
Unadjusted incidence rate	4 (2.9%)	10 (3.5%)

Relative Risk: Celecoxib vs. Placebo = 1.21

Primary CV events:  
 1. Cardiac death: myocardial infarction, myocardial infarction, unstable angina, cardiac arrest, thromboembolism  
 2. All-cause mortality including subarachnoid hemorrhage or other cardiac death, and  
 3. Fatal and nonfatal thromboembolic events: pulmonary or femoral-popliteal thrombosis, thrombotic thrombocytopenic syndrome, stroke, embolism



## COX-2 Inhibition by Rofecoxib & Celecoxib At Steady State†

(LPS-Induced PGE<sub>2</sub> Whole Blood Assay)  
Day 7 Weighted Average Inhibition



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