

Question 8: CV Evaluation of New NSAIDs

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

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Highlights

- **SIMILAR STANDARDS AS FOR MARKETED NSAIDs:** Dr. Wood said that the standards for trials of new NSAIDs should be just as stringent as for marketed NSAIDs. Dr. Fleming said that the previous sample size recommendations (“rule out a 50 percent increase in the relative risk for cardiovascular events”) should be applied to new NSAIDs.
- **DO TRIALS IN SETTING OF CV RISK REDUCTION STRATEGIES:** Dr. Holmboe reiterated, for trials with new NSAIDs as well as marketed drugs, that standard cardiovascular risk reduction strategies be employed, since this is a setting where the drugs might be increasing cardiovascular risk.
- **SWITCH CURRENT COX-2 PROGRAMS AWAY FROM DICLOFENAC:** Dr. Nissen said that the current investigational COX-2s should change their development programs to use naproxen as the comparator rather than a non-coxib COX-2 selective drug such as diclofenac.
- **POWER FOR SUB-GROUP & DURATION ANALYSES:** Dr. Gardner commented on the need for adequate power for subgroup analyses and duration-of-use analyses.
- **TARGET POPULATIONS BUT NOT HIGH CV RISK PATIENTS:** Dr. Farrar said that the trial populations should those in which the drugs will be used, while “obviously limiting it to” mild cardiovascular risk.
- **COMPARATOR SHOULD UNCLUDE NSAID+PPI:** Dr. Farrar also said that one of the comparisons should be of GI toxicity versus a comparator that has a gastroprotective component such as a PPI.
- **NEW SAFETY PARADIGM WILL SLOW DRUG DEVELOPMENT:** Dr. Cush said that for new drugs, low-risk patients with the indication being sought should be studied versus an active control for 1-2 years. He also pointed out that a requirement to complete an adequate long-term safety trial

before a new NSAID can be marketed is a “departure in process” and “may take a longer time to do”. Dr. Jenkins confirmed that this is what he thought the committee was advising. Dr. Cush expressed concern that future drug development not only for NSAIDs but in other therapeutic areas might be “delayed and curtailed” because of “this new paradigm”.

- **DRUG DEVELOPMENT MAY BE SLOWED IN OTHER AREAS ON CASE-BY-CASE BASIS:** Dr. Nissen thought that the NSAIDs were a special case and similar standards need not necessarily be imposed for other drug classes. Dr. Temple agreed but also said that similar special situations existed (because of “priors”) with heart

failure drugs (where long-term survival trials are needed) and with anti-arrhythmic drugs (in which the CAST trial showed that these drugs could have “a disastrous outcome”). Dr. Wood said another example was phosphodiesterase inhibitors.

- **INCREASED SAFETY REQUIREMENTS ARE NOT JUST CARDIOVASCULAR:** Dr. Wood said it was not just cardiovascular risk that had to be evaluated satisfactorily but also “heart failure” , “GI bleeds” and “complicated ulcers”. Dr. Temple commented that some sponsors of coxibs have “seen that particular handwriting on the wall” and are trying to do studies of this type.

Discussion of Question 8

DR. WOOD: Question 8: With regard to evaluation of cardiovascular risk, what studies do you recommend as essential to be completed and reviewed prior to approval of new NSAIDs. With regard to the evaluation of the potential benefits--for example, reduced G.I. risk--what studies do you recommend as essential to be completed and reviewed prior to approval of new NSAIDs? Please be specific with regard to trial design, patient placebo, control groups, endpoints, duration, sample size, safety monitoring and patient protections, et cetera? Some of this, actually, John, we have already covered. I think, in the studies that we recommended for the "get out of jail free" cards, we have covered that. So we could go back over that, I think, and see if there are additional things we wanted to do. We

have covered some of these already. Yes?

DR. HOLMBOE: I just want to reiterate one thing I would suggest that applies to the previous studies discussed and to new studies. Again, I want to emphasize that, if we are going to do a randomized controlled trial, our hypothesis is that these drugs are causing harm. Therefore, you are being randomized to harm, not benefit. I would just make a plea that, if you are going to do these studies, as has been discussed using the various comparators, that we maximize, as part of that trial, the cardiovascular-risk-factor reduction, getting to Dr. Hennekens' point. I think not to do that would be unethical.

DR. GROSS: Any other comments? Yes; Dr. Nissen?

DR. NISSEN: Again, this is really challenging. I know what I am going to say isn't going to be popular with the Merck folks, but I just don't think that--I think you have got to have a comparator that is neutral or better than neutral. So I want the new drugs to show an upper confidence boundary in the range of what Tom Fleming talked about against naproxen. That is a high enough standard to protect the public which is what we are all talking about here today. So I am willing to accept that naproxen is no worse than neutral. So, if you are not 50 percent worse than naproxen, then you meet a standard that I would consider acceptable and then that is going to be a point estimate that is no more than about a 15 or 17 percent worse than naproxen. That is a safe and secure way to proceed. Now, that means restarting some development programs. I know it is very painful, but I don't think that being as good as diclofenac when we don't know how good diclofenac is, is the right standard.

DR. HENNEKENS: I agree with you, completely, Steve. I think the same bar should hold for any of the new NSAIDs.

DR. GROSS: Dr. Gardner?

DR. GARDNER: I think all the studies should be powered adequately for subgroup analysis and to have duration of use taken into account so that we can make some of these distinctions that we have been struggling with.

DR. GROSS: Dr. Farrar.

DR. FARRAR: Two quick but different points. One is that we need to be very careful that the drugs are tested in populations in whom they are likely to be used, namely patients who are older and have either hidden or, perhaps, some mild known cardiovascular risk, obviously limiting it to people with mild risk, but in the group in which it is likely to be used. The second issue is, you ask about the G.I. benefit. I do think that, given all the talk that we have gone through these three days, that it would be appropriate for any new drug to have a comparison against naproxen or one of the other COX-1s in combination with a protective agent for stomach ulcers. That combination, obviously, would need to be discussed.

DR. WOOD: I would say that we should certainly insist on at least the studies that we recommended before and that we should consider comparisons to naproxen and, if there is an appropriate indication, and to placebo if we can do that. Once we have got a naproxen PPI and placebo study in our bag, we would be in a lot better shape to interpret what we are actually looking at, I think. Dr. Fleming?

DR. FLEMING: I would just echo what has been said previously that I would want to see, depending on the indication, it could be placebo control, it could be naproxen control, evidence that essentially allows us to rule out a 50 percent increase in the relative risk for cardiovascular events.

DR. WOOD: Dr. Cush?

DR. CUSH: I think it is important to be practical. So, for new drugs not yet on the market, they should be required to do

these trials just like APPROVe and CABG II with valdecoxib except these must be done in the indications for which a drug is being sought, so in osteoarthritis, in rheumatoid arthritis, or whatever, and that those trials should be done in low-risk individuals, that they should not be done in high-risk individuals, because, otherwise, you really shouldn't be using these drugs in high-risk individuals. So they should be done in low-risk populations and they should be done with an appropriate active control group over a long period of time, which is at least a year, but I think it would be preferable to do two years. These will be difficult and expensive trials to do but they must be done for those who want to come into the market. For those that are currently in the market, I think that the answer could probably be helped a great deal by Dr. Temple's ALLHAT design or a modification thereof.

DR. WOOD: Any other comment on that? Is that helpful, John?

DR. JENKINS: Yes.

DR. WOOD: What is your pleasure? We are losing people so what is your pleasure for the next question? 9?

DR. JENKINS: I think 9 is getting us into the area of--it is fairly speculative and, in many ways, linked to No. 6 where you have already recommended that there be something in the labeling about products that don't have data. So I don't know that 9 is critical because, obviously, any future NSAID that we get is likely to come back to this committee for your recommendation before we make an approval decision. So then we would actually have the data in front of

us to decide what the labeling should say.

DR. WOOD: So do you want to go back to 7, then?

DR. FLEMING: Before we do, can I make one comment?

DR. WOOD: Yes; Tom.

DR. FLEMING: Basically, on 9, you are putting forward a potential condition upon which, if satisfied, could lead to the absence of a label indicating a warning. The critical distinction here is this is worded as, if there is absence of establishing an increase, which is very different from evidence against an increase, and that is basically failure to achieve statistically significant establishing an increase is not ruling out an increase. So this first sentence here--if you do trials that fail to show significant increases, that is not a reassurance against an increase. What you want is evidence sufficiently powered and sufficiently neutral ruling out unacceptable increases. That is a critical distinction. So the essence here is--I think the first sentence is very misleading as to the basis for removing the need for a black box. It is what we have been saying when we have been talking about Question No. 7. What we would want is evidence sufficiently favorable and adequately precise that you can rule out an unacceptable increase. And some of us have put forward a suggestion that that could be a relative risk of 1.5. So if studies are done of sufficient quality and sufficient size and sufficient precision with sufficiently favorable results that you can rule out a 50 percent increase, then I think it logically follows to then suggest that that

would justify a substantial weakening of the precautions that would have to be in the label.

DR. JENKINS: Thanks for that clarification. The idea was that whatever studies you recommended in Question 8 carried over to the findings that would then impact on the labeling in Question 9. So maybe the wording is imprecise but, if you are recommending that rule out 50 percent increase in Question 8, then 9 is--if we get that rule-out 50 percent increase, would that, then, result in something less in labeling than the others have.

DR. FLEMING: The essence of my point is it is not persuasive simply to say that we did trials that failed to show an excess. Rather, we need trials that rule out unacceptable increases.

DR. WOOD: I think we were saying, also, John that the studies we recommended in Question 5 all that we learned from that would carry over to this as well. At least that is what I thought we were saying. I was sort of, I guess, piggy-backing onto Tom's and my comments at that stage. Richard?

DR. PLATT: I would like to make a comment about Question No. 7, if I may.

DR. WOOD: No. which?

DR. PLATT: Question No. 7.

DR. WOOD: Wait a minute. Before we do that, are we finished? We are not going to do 9. Is that what you are saying, John?

DR. JENKINS: I think you are having some discussion about 9 now. You have

kind of clarified what you would like to see as far as the pre-approval databases. Dr. Fleming just helped clarify his thoughts, at least, on if those pre-approval databases meet the criteria that he established, it sounds like he wouldn't think that they would have to carry the same level of warning that the approved products are going to be getting.

DR. WOOD: I think the other point, which I think he made as well, but just in case it was missed, is there is also a duration period. We would expect to see sufficient sample size and sufficient duration of exposure in these trials before approval which is not the case with some of the drugs we have right now.

DR. JENKINS: Right.

DR. WOOD: Dr. Cush?

DR. CUSH: I just want to ask Dr. Jenkins and Dr. Temple, you are now suggesting, by this question, as a condition of future approval for future agents that this cardiovascular safety study would have to be completed prior to granting and considering a new drug application.

DR. WOOD: Absolutely, I think.

DR. CUSH: Because that is, obviously, a departure from what we have done. These are usually--of course, this trials would have safety issues as the primary endpoint, not efficacy, so it may take a longer time to do. Again, that is a departure in process, is it not?

DR. JENKINS: I think what the committee, so far, seems to be recommending for new products in this

class of NSAIDs, you are essentially saying there needs to be an outcome study prior to approval, outcome meaning that cardiovascular and probably also the G.I. outcome study so you can really assess benefit:risk before the approval decision. So that is a departure from what was required in the past for this class of drugs where we heard people did 3, 6 or 12-month efficacy trials and had databases of 4,000, 5,000 patients. But they didn't have an outcome study specifically powered to rule out some degree of cardiovascular risk or to specifically evaluate the complicated G.I. leading issues.

DR. WOOD: It is not just cardiovascular risk. It is heart failure. It is G.I. bleeds. It is complicated ulcers. It is the whole gestalt of risk that we are talking about, it seems to me.

DR. TEMPLE: You can see from some of the presentations that some companies marketing COX-2-selective drugs have already seen that particular handwriting on the wall and have done those very studies, not necessarily perfectly.

DR. CUSH: I agree. But my concern is it is setting a new paradigm for clinical trials in the United States, that we actually now have to do trials for severe and worrisome, albeit common, side effects prior to the approval of a drug. I am not so concerned about non-steroidals. I am concerned about future drug development in other areas where novel medicines may be delayed and curtailed as far as development because of this new paradigm.

DR. NISSEN: Let me answer that and say that this is different. The reason it is

different is that the disease we are talking about is the leading cause of death in the United States. It is vascular disease. So it is very common. We have got a lot of evidence that several drugs in this class can substantially elevate the risk of that very common and lethal disease. We are not saying this is the regulatory standard for every product and every class. The other reason why we can afford to do this is we have alternatives here. There are 20 drugs on the market. We are leaving on the market some coxibs with some warnings. So the patient and the physician have a lot of choices. So it is okay to now set a pretty high bar because that is what we really need to do, now that we know what we know. We learned it the hard way. We learned it via a very, very difficult process that took place last fall. Now that we know that, we know where to set the bar for this class of drugs and it has to be set pretty high.

DR. TEMPLE: There is a lot of public discussion going on about how safe things have to be. But what Steven said is absolutely right. You have got priors here. There are other examples of this. I will very briefly give you two. If you want a drug for heart failure other than, perhaps, an ACE inhibitor or something like that that we think we understand, we will expect an outcome study, a survival study, because so many drugs for heart failure have had adverse outcomes while improving exercise tolerance. Similarly, any new antiarrhythmic drug has to provide similar data before it can be approved. That is not a good situation--it is not a good thing for drug development of those drugs, but we have had a disastrous outcome, CAST. So where

you have priors, you modify your expectations.

DR. WOOD: These were the examples I was going to give. I think we are in exactly the same situation here, Bob. We have been through the process. We have gained the experience. And we are in the same way as we are with phosphodiesterase inhibitors. If another phosphodiesterase inhibitor came along, we would view it somewhat skeptically.

DR. TEMPLE: Right. I think that is the point Steve was making, too.

DR. WOOD: Exactly.

DR. TEMPLE: We know something here.

DR. WOOD: We are going to move, then, to Question No. 7 and start with that.

Slide with Text of Question 8

8. With regard to evaluation of cardiovascular risk, what studies do you recommend as essential to be completed and reviewed prior to approval of new NSAIDs? With regard to the evaluation of the potential benefits (e.g., reduced gastrointestinal risk), what studies do you recommend as essential to be completed and reviewed prior to approval of new NSAIDs? Please be specific with regard to trial design, patient population, control groups, endpoints, duration, sample size, safety monitoring and patient protections, etc.