

# Committee Questions for Dr. Lyketsos on ADAPT Trial

## 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

- **FIRE IN AUDITORIUM:** Dr. Nissen commented that the initial NIH announcement was “the medical equivalent of screaming ‘fire’ in a crowded auditorium” and it would have been preferable to have said that the trial was being stopped for “for futility rather than for hazard, when there was a non-statistically significant hazard”. Dr. Wood and Dr. Gibovsky agreed with this comment.
- **GI BLEED COMPONENT:** Dr. Farrar asked about the advisability of a trial that put “patients at risk of .... serious complications from the G.I. bleeding”. Dr. Lyketsos said that the GI risk was considered in the context of the high risk of these subjects for the “devastation that Alzheimer's disease brings”.
- **USE OF PREVENTION DATA TO RESTRICT TREATMENT USAGE:** Dr. Gibovsky asked about restriction of drug use for treatment purposes being based on results in a trial for prevention of disease. Dr. Lyketsos said that on this point he would “defer” to “people who are more expert in that”.
- **BASIS FOR DOSING DECISION :** Dr. Fleming said that it was his understanding that the “driving issue” behind the steering committee recommendation came from “the external data on the APC trial for Celebrex” and not “some emerging trends that happen to be in the unfavorable direction on naproxen”. He put this in the context that “one has to be extremely cautious, when you are looking at data continually over time, not to over-interpret emerging trends that can easily ebb and flow”. Dr. Wood said: ‘Just to develop that question, what I understood you to say was you hadn't passed some stopping boundary; is that correct?’
- **PRACTICALITIES VERSUS EVIDENCE:** Dr. Lyketsos responded that “the issue really was one of practicalities more than our internal data” including talking to “IRBs and participants”. Dr. Fleming asked that Dr. Lyketsos clarify “what your sense of the evidence was”

before discussing practicalities. Dr. Lyketsos said that in the context of the “climate” created by the removal of Vioxx from the market and “the widely publicized APC results”, they “had to stop and take stock and get more information” even though their own results “did not compel us to stop treatment based on our own data”.

- **EXTERNAL NAPROXEN DATA MIGHT HAVE ALLOWED CONTINUATION:** Dr. Fleming said that they did have access to the “VIGOR data which was very reassuring for naproxen” and he was “perplexed” as to why the steering committee decided not to continue the study when “your data-monitoring committee, in looking at the data, looking at the benefit as well as the risk, indicated the study should continue”. Why did they not pursue a strategy of notifying investigators, IRBs and patients “that the monitoring committee has carefully looked at benefit and risk and that the totality of the data is beyond the APC trial” since the concern in the ADAPT trial was a possible safety problem with naproxen and not celecoxib.
- **STEERING COMMITTEE ACCESS TO DATA IS VIOLATION OF TRIAL MONITORING PRINCIPLES:** Dr. Lyketsos said that “some members of the steering committee did have access to the data that the DSMB had seen” and that such “very difficult judgment calls” have to take into account “evidence, but also practical aspects of continuing to conduct this sort of a prevention trial ....”. Dr. Fleming said that he was “dismayed to hear ... some steering

committee members, had access to the data. That is also a violation of the principles of monitoring trials. It should have been in the sole possession of the data-monitoring committee. I am also distressed because I am not hearing that the monitoring committee was front and center in terms of having these issues brought back to it for reassessment ....”.

- **DROPOUT RATES AFTER VIOXX WITHDRAWN:** Dr. Wood asked for clarification if “one of the perceptions was it was no longer possible to continue the trial” because “of a very large number of dropouts from the trial after the Vioxx withdrawal”. Dr. Lyketsos said that “adherence” had been declining annually and “that now there were data about one of the study drugs”, “that would further erode adherence”.
- **CLARIFICATION: DRUGS STOPPED FOR OPERATIONAL PROBLEMS RATHER THAN SAFETY:** Dr. Wood said that the initial announcement “was that this trial was being stopped for a safety signal” but what “I heard in your statement and what I hear from you now is that the trial was being stopped for operational problems...”. Dr. Lyketsos responded that “I think my statement should speak for itself. In terms of what the data were, as I have pointed out, they will be submitted very soon so that you can judge for yourselves”.
- **NAPROXEN MAY HAVE CARDIOVASCULAR RISK AND ADAPT TRIAL RESULTS MAY CLARIFY THIS ISSUE:** Dr. Farrar said that the ADAPT study will “provide some vitally important

information” on naproxen and he questioned Dr. Fleming’s comment about the VIGOR trial providing “some reassurance about naproxen” since VIGOR provided no information against placebo. Dr. Farrar said that “I have assumed, based on all the data that we have, that every NSAID will not fare well against a placebo” in terms of

cardiovascular safety, and “this study is likely to provide the data to support that”.

- **LESSONS FOR THE FUTURE:** Dr. Nissen made the final comment that “it caused a panic that was unnecessary and it shouldn't have happened, and I hope it doesn't happen again”.

## Presentation Text

DR. WOOD: Thank you very much. Are there questions directed to the speaker? Dr. Nissen?

DR. NISSEN: I fully understand your rationale and I understand that the trial was fundamentally stopped because of an issue of futility. You didn't think that you could keep people in the celecoxib arm. That is all well and good. The problem that occurred here is that a warning was issued on naproxen which had the effect of being the medical equivalent of screaming "fire" in a crowded auditorium. All over the country, many of us got calls from patients saying, "I want to stop my naproxen because it causes a cardiovascular risk." I think, just a comment here, that it would have been far better to have announced that the trial was suspended for futility rather than for hazard, when there was a non-statistically significant hazard. So, one man's comment.

DR. WOOD: I agree with that. Any other comments? Yes?

DR. FARRAR: I wonder if you could comment on the G.I. bleed component since, obviously, one of the deliberations we have to undertake is the relative problems with G.I. bleed versus cardiovascular risk. Certainly, that was known a priori before starting the study. As you commented very carefully, that wasn't the only consideration. But, in a drug trial where the outcome is unknown and the risk is really fairly well known, I wondered how you thought about that in terms of putting patients at risk of something on the order of a few percentage over the course of a five-year trial who might have serious complications from the G.I. bleeding.

DR. LYKETSOS: I guess you are asking me a human-subjects question.

DR. FARRAR: I am asking how, in the design of the study, obviously the choice was made to accept that risk for the unknown potential benefit of reduction in Alzheimer's disease over the course of the same trial. I am wondering if you have any insights into how that decision was made because, clearly, there are

issues there about the use of these drugs and their risks.

DR. LYKETSOS: Well, I am glad you are asking the question. It certainly is an issue that we have spent a lot of time discussing and which we discussed with study sections, IRBs, at quite some length and continue to discuss. I think the fundamental point that I would start with is where I started my presentation which is the devastation that Alzheimer's disease brings and the fact that all the study participants were individuals who had a first-degree relative with the disease and had, therefore, personal experience. In that context, we were very careful and very clear with them about what we thought at the time the known G.I. risks were so that, in the process of consent, and that was revealed through careful discussions in the consent process as well as the consent form, the risk of G.I. bleed was stated very clearly and that that, in some cases, might lead to death. So I think we felt that this was a decision that our participants could make, given that the risks were relatively small, and the risk that they would develop Alzheimer's disease was higher and that we felt they could make the decision for themselves if they were willing to take the risk:benefit calculus as we saw it.

DR. WOOD: Dr. Gibofsky?

DR. GIBOFSKY: I share Dr. Nissen's concern about this effect of crying fire in a crowded theater. Many of our patients called and suggested that they were going to stop their celecoxib because of the concerns that were raised from ADAPT as well. But you raised a very interesting concern that I confess I hadn't given enough thought to and that is the

difference between a prevention trial and an outcome trial. Much of our discussion here later today, I suspect, is going to focus on what action should be taken, if any, to restrict drugs based on treatment from data on prevention trials. I would be very curious to hear you expound on that a bit more.

DR. LYKETSOS: That is an interesting question. Let me just, if I could, because there have been three comments now--I just would like to refer you to the early part of my statement where I said the presentation is important because there is much public misunderstanding about our decisions and their rationale. Several of you pointed out that there was a cry of fire. I don't believe that that came from the study.

DR. WOOD: We won't ask you to speculate where it came from. There is certainly a view on that.

DR. LYKETSOS: I am not sure where it came from. But, to address the other issue, I must say I have not given it much thought as to whether prevention-trial safety data would generalize in the way that you are thinking about it. So I will defer on that because I think it would need a fair bit more thought by people who are more expert in that.

DR. WOOD: Dr. Fleming.

DR. FLEMING: It is my understanding, from what you are saying, that the steering committee was particularly influenced by the APC prior data not by the internal data from ADAPT; i.e., there were, from what you were describing, some emerging trends that, in my words, were in the unfavorable direction but in the context of monitoring trials, we

know that one has to be extremely cautious, when you are looking at data continually over time, not to over-interpret emerging trends that can easily ebb and flow. So my understanding, from what you are saying, is it wasn't that there were, at this point, some emerging trends that happen to be in the unfavorable direction on naproxen. Rather, it was the external data on the APC trial for Celebrex that was the driving issue behind the recommendation.

DR. WOOD: Just to develop that question, what I understood you to say was you hadn't passed some stopping boundary; is that correct?

DR. LYKETSOS: I'm sorry? I didn't hear the first--

DR. WOOD: You hadn't violated your stopping rule, or whatever stopping rules, you had for safety.

DR. LYKETSOS: I think that our TEMC, our DSMB, had opined the week before with the same data from within the trial that they felt that we should continue. So it was interesting how the two events were back-to-back.

DR. FLEMING: I would like to come to that second. I am leading to that. But first I wanted to make sure that I understood what was the nature of the concern. Is my interpretation correct?

DR. LYKETSOS: I think so. Back to how I put it, the issue really was one of practicalities more than our internal data, is that we felt we would have to talk to IRBs and participants and tell them something about--

DR. FLEMING: Could I first understand what your sense of the evidence was. I want to discuss that first, versus the practicality.

DR. LYKETSOS: The sense of the study evidence.

DR. FLEMING: The sense of the evidence that was the basis for the decision in terms of adverse effects. I have heard two things. One is the naproxen, but that was not compelling evidence. That was within the framework of emerging results that could be by chance alone when you are monitoring data frequently. But external APC data was very influential to you. That is what I am hearing. Is that correct?

DR. LYKETSOS: Well, in fact, we didn't know all the details of the APC data, as I pointed out. I think it was that plus the climate that had been created by rofecoxib coming off the market, the influence that that had to some extent on our participants, then the widely publicized APC results and the sense that, even though the data we were seeing and that our TEMC the week before had seen, did not compel us to stop treatment based on our own data, that there was now a climate created where, practically speaking, we had to stop and take stock and get more information, et cetera. So it was that sort of the decision. I was a complicated decision and that is why it takes a three-page statement to try and explain what went through our minds.

DR. FLEMING: There may not have been, to the steering committee at this time, access to data on PRECEPT for celecoxib or to the etoricoxib, the

lumiracoxib, data on naproxen that were very favorable, but you did have access to the VIGOR data which was very reassuring for naproxen and you had evidence from the CLASS trial and some other data from Celebrex. I am perplexed that you would look at the totality of these data and say that the results were conclusive in terms of at least not being able to provide information to the IRBs and to the patients and caregivers in the trial representing the totality of the data when your data-monitoring committee had looked at the totality of the evidence for benefit to risk. On a data-monitoring committee, I have always argued, don't just show me the safety data, even if we are just looking at early assessments for safety. It always has to be benefit to risk. Even though, as you are pointing out, this wasn't a therapeutic setting, prevention trials also provide major opportunity for benefit. Preventing major diseases is also a very significant benefit. My understanding is your data-monitoring committee, in looking at the data, looking at the benefit as well as the risk, indicated the study should continue. How did the steering committee judge, without access to ongoing data, that benefit to risk couldn't be sufficiently favorable and that a notification to the investigators, to the patients and to the IRBs, that the monitoring committee has carefully looked at benefit and risk and that the totality of the data is beyond the APC trial when you are looking at Celebrex and naproxen? Why wasn't that strategy pursued?

DR. LYKETSOS: First, as I pointed out in my statement, some members of the steering committee did have access to the data that the DSMB had seen. That is the first point. The second point is, as

you point out and as I think this whole discussion points out, is these are very difficult judgment calls. They have to take into account evidence, but also practical aspects of continuing to conduct this sort of a prevention trial in this sort of a population. I think it was the judgment call, and I can tell you, there was substantial discussion around this when we had the steering committee meeting, about these very issues. It was the collective judgment at the time that this was the right thing to do, given the various issues that I have articulated in my statement.

DR. FLEMING: I will just pursue one more. I am dismayed to hear the steering committee, some steering committee members, had access to the data. That is also a violation of the principles of monitoring trials. It should have been in the sole possession of the data-monitoring committee. I am also distressed because I am not hearing that the monitoring committee was front and center in terms of having these issues brought back to it for reassessment. So, to me, what I am hearing raises very significant concerns about putting at risk the integrity of studies with prejudgments using only access to partial external information.

DR. WOOD: There was one other thing, though, at least the word on the street was, and you sort of mentioned that as well, I understood there was a very large number of dropouts from the trial after the Vioxx withdrawal and others and that one of the perceptions was it was no longer possible to continue the trial. Is that true?

DR. LYKETSOS: Let me clarify that. The adherence had been declining on an

annual basis even before rofecoxib was withdrawn from the market. So adherence was perceived as an issue in that we felt that now there were data about one of the study drugs and that that would further erode adherence. We did not see a huge erosion in adherence with rofecoxib, specifically, but there had already been an erosion that was concerning and we anticipated a further erosion.

DR. WOOD: Right. But the question for this committee that Dr. Fleming is pursuing vigorously, and I agree with him, is that the announcement that you all made--the announcement, as it was picked up--maybe I should put it like that--was that this trial was being stopped for a safety signal. What I heard in your statement and what I hear from you now is that the trial was being stopped for operational problems in the trial and the safety signal was a convenient moment at which to do that. But you had operational difficulties. That is a very different interpretation and a very different interpretation for the public and patients. Is that what you are hearing, Tom?

DR. FLEMING: It certainly appears to be. It is part of what is concerning to me.

DR. LYKETSOS: I think my statement should speak for itself. In terms of what the data were, as I have pointed out, they will be submitted very soon so that you can judge for yourselves.

DR. WOOD: Okay. Any other questions? Sorry; Dr. Farrar. I beg your pardon. Dr. Farrar, go ahead.

DR. FARRAR: I think, actually, that this study provide some vitally important

information with regards to our consideration of the entire class of drugs; namely, the NSAIDs. I would like to just read one sentence from the statement. It said, "Although some post hoc data composites barely reached statistical significance for naproxen versus placebo." Now, clearly, this discussion would be much clearer after the presentation of the data, a careful review of the data. But Dr. Fleming noted that, in the VIGOR study, there was some reassurance about naproxen. I would like to just question that. What is very clear in the VIGOR study is that naproxen was safer than rofecoxib. But it does not comment at all with regards to the potential risk compared to placebo. In fact, I was surprised when I heard the statement by Dr. Fleming because, in fact, I have assumed, based on all the data that we have, that every NSAID will not fare well against a placebo. I think that this data, and probably will be supported by the publication although I don't want to try and foresee the future, but my guess is that naproxen will not fare particularly well against placebo in terms of its cardiovascular safety. I think we need to be able to accept the fact that all of them have some risk with regards to cerebrovascular disease and this study is likely to provide the data to support that.

DR. WOOD: Dr. Nissen?

DR. NISSEN: I don't want to belabor this because we have got a lot more to discuss today, but I think it is extremely important that, as a medical community, we learn from this episode. In the kind of media frenzy that was going on during that period of time, this announcement, this warning that was issued on a national basis about

naproxen, was inappropriate, led to some panic amongst the public and we simply can't do business this way. We can't operate in this kind of a fashion. I would urge any of the individuals who were involved in the decision to issue a warning to go back and look at what happened and try to ensure that we don't do this sort of thing again, because once this gets picked up by the media, it passes through generations of people and becomes the topic of extensive discussion and may lead patients who don't have the ability that we have around this table to filter data--they don't understand data-safety and monitoring boards. They don't understand stopping rules. And it caused a panic that was unnecessary and it shouldn't have happened, and I hope it doesn't happen again.