

Valdecoxib Discussions: Dr. Furberg and Pfizer

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

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Highlights

- **INCONSISTENCIES:** During the valdecoxib discussion period on Day 1, Dr. Furberg said he was “troubled by some inconsistencies that I have found in the briefing document from Pfizer”. It was agreed that Pfizer would review these issues and respond during the Day 2 proceedings. After the end of the Day 1 proceedings, Dr. Furberg and Pfizer met to go over the issues.
- **LACK OF RESOLUTION REPORTED DAY 2:** At the discussion of the matter on Day 2, Dr. Furberg said that “We met and I got some clarification, but I continue to be troubled.” Dr. Wood, the Chairman, suggested that Dr. Furberg “tell us about the issues and let's give Pfizer an opportunity to respond.” Dr. Furberg said that there were 5 issues.
- **ISSUE 1:** Dr. Furberg’s first issue was the number of trials reported in the acute pain integrated safety analysis. Dr. Harrigan (Pfizer) responded that Pfizer presented two separate data groupings (on pages 55 and 76 of the briefing document).

One grouped 18 studies with a daily dose range of 20-60 mg. The other grouped 20 studies with a daily dose “greater than 20 mg total daily dose”. The difference between these two groups of studies was “largely due” to the fact that one grouping did not include “the CABG Study 035, which is described in great detail, in fact, six pages devoted to the CABG studies in the briefing document.”
- **ISSUE 2:** Dr. Furberg’s second issue dealt with the number of cardiovascular events reported in the integrated safety analysis. This depends partly on the definition (whether you include sudden death as well as fatal CHD) but the numbers did not seem to add up. Pfizer told him that “in the second CABG trial that got involved in the analyses, they subtracted the number of events when the patient was on the I.V. formulation parecoxib”. However, “I looked it up and it turned out to be one case. So, that doesn't explain the discrepancy, so the explanation that was given was not satisfactory.” Dr. Harrigan

responded that since patients received parecoxib first and then valdecoxib, you “have to assign the event to one treatment or the other, they were appropriately assigned to parecoxib, and so they are not accounted for in the valdecoxib column.” Another reason for the discrepancy depends on whether adverse events were adjudicated or not.

- **EVENT ALLOCATION TO VALDECOXIB OR PARECOXIB IF DURING PARECOXIB THERAPY:** Dr. Wood commented that since ‘parecoxib is the pro-drug for valdecoxib’, “as far as my body knows when it gets parecoxib, it has got valdecoxib”. Dr. Harrigan asked if Dr. Wood was suggesting that “all patients that receive parecoxib be transformed to valdecoxib”. Dr. Wood responded ‘I guess the body transforms it to valdecoxib’. Dr. Harrigan said ‘It would obscure the data from the effects of parecoxib,

which is given by a different formulation”.

- **PFIZER STATEMENT ON SAFETY DATA REPORTING:** Dr. Harrigan said ‘It is important to us that members of this committee and the FDA, and other health agencies worldwide understand that we do not suppress safety data. We report safety data. We report it in a number of different ways. We do not suppress safety data.’
- **ISSUE DEFERRED TO FDA FOR RESOLUTION:** Dr. Furberg commented “The numbers just don't add up”. It was agreed that the issues would be deferred to FDA for resolution. Dr. Furberg said “... it would be much better if you explained why you did it differently”. “I think there are some numbers that will be hard to explain away.” Dr. Wood said “I think we have got it that there is still a bone of contention here.”

Discussion Text

Day 1 Session:

DR. WOOD: Curt?

DR. FURBERG: Well, I am troubled by something else. I am troubled by some inconsistencies that I have found in the briefing document from Pfizer. I would like to just briefly go over some of them. On page 55 there is a summary from acute pain studies. It says here are the safety data from 18 clinical studies. On page 76 in the summary it says here are the safety data from 20 completed

studies. I just wonder what happened to the other two trials. They disappeared. Any suppression of information or is it just an error?

DR. VERBURG: We will check on that.

DR. FURBERG: The other thing relates to the overall findings from these summary studies, the 18 studies. In Table 19, on page 60 for acute myocardial infarction it says placebo, 0;

valdecoxib, 3. In the following table for myocardial infarction it says 1 versus 3. So, there is an internal inconsistency in two tables after each other. What is even more striking is that when you start looking at the individual studies that contributed to the summary statistics for the 18 studies--I just looked at two of them, the study we just talked about, the general surgery study. In terms of myocardial infarction, depending a bit on how you define it, there were 3 and 2. If you include cardiac arrest and sudden cardiac death it is 6 to 0. The summary statistic was 0 to 3 or 1 to 3 and here I have 6 in one study. I add in the data from one of the bypass surgery trials and I get additional numbers. So, just by combining the bypass surgery trial 071 and the general surgery for MI I have 0 to 8 or 1 to 9; not 1 to 3. And how about the other 16 studies? That is troubling. I also find that they included in the summary statistic one of the bypass surgery trials but not the other one. Why? I mean, the other study met the same definition. If you put that in the numbers get even worse. So, there is clearly an under-reporting of events the

Day 2 Session

DR. WOOD: One of the things that we left undone from yesterday was that Dr. Furberg raised some issues that he was unclear of some differences that he thought he saw in the Pfizer briefing book and from his calculations. I charged him with meeting with Pfizer and trying to resolve these. Dr. Furberg, did that get resolved?

way I interpret it, and I have to say that we all make mistakes, and most of them are honest. Honest means that sometimes you benefit from your mistakes and sometimes you are hurt. But here all the inconsistencies tend to go in one direction. So, I just raise the question whether these are honest mistakes. It has made me wonder how much trust I can have in the information that we have received.

DR. WOOD: Dr. Hoffman?

DR. HARRIGAN: Excuse me--

DR. WOOD: All right.

DR. HARRIGAN: This is Ed Harrigan from regulatory affairs at Pfizer. We would like to have ten minutes. We are not prepared at this point to go through table by table to look at the questions that you have. We would like ten minutes tomorrow to do that and I think we will quite readily answer all the questions you raised.

DR. WOOD: Okay, that is helpful.

DR. FURBERG: We met and I got some clarification, but I continue to be troubled.

DR. WOOD: So, the answer is no I guess. Why don't we do this then.

DR. FURBERG: I think there are five issues.

DR. WOOD: Why don't you tell us about the issues and let's give Pfizer an

opportunity to respond. Curt, why don't you go through the issues as you see these.

DR. FURBERG: The first one related to the number of trials included in the integrated safety analysis for the acute pain studies. There was in one place mentioned that there were 18 trials, in another place there were 20, and the explanation that was given was that the 18 trial analyses excluded 2 trials, the one using the highest dose of the drug, 60 mg--more than 60 mg a day. That doesn't satisfy me. If you are looking at safety, the trials with the highest dose are the ones that I am primarily interested in. I think the company did the proper thing, they included information about that, but they should have included that in the pooled analyses, as well, and that would have changed the message that you take away from that summary table. So, that was one issue.

DR. WOOD: Let me ask Pfizer, do you want to respond to each one in turn, is that the easiest way?

DR. HARRIGAN: That would be fine with me.

DR. WOOD: Let's do that, then, we can see what the issues are.

DR. HARRIGAN: Just one slide, slide D114, please. Ed Harrigan from Regulatory Affairs, Pfizer. What we have done with this slide is basically pulled the two paragraphs from the briefing document that Dr. Furberg was describing. In Section 3.3, anybody who has the briefing document and who downloaded it from the web would be able to find these on pages 55 and 76. So, in Section 3.3, as Dr. Furberg points

out, we integrated safety data from acute pain studies, 18 of these studies, and as it says in the paragraph, they represented 4,087 patients treated at a dose range of 20 to 60 mg total daily dose. Later, in Section 3.6, we described 20 completed studies representing a larger number of patients treated with valdecoxib at a dose range greater than 20 mg total daily dose. Now, the difference between these two paragraphs is largely due to the CABG Study 035, which is described in great detail, in fact, six pages devoted to the CABG studies in the briefing document. It is a matter of opinion as to whether one should have pooled this data. If one had pooled all the 80 mg data, then, one might have been accused of diluting the 80 mg treatment effect that was seen in the CABG 035 study. On the other hand, the 035 study was presented by itself with full representation of the safety issues in that study, which have been discussed in great detail here in the committee, appropriately so. I think that is probably the end of response to that point.

DR. FURBERG: The second issue is to the mean consistency in the reported event data. Again, we are back to the same integrated safety analysis of the 18 studies, and Tables 19 and 20 indicate that there was a total of 4 to 6 MIs depending on how you define them, whether you include sudden death in the report. Well, separately, there were data presented on two of the trials that were included among the 18, and I just added up the number of MIs and I come up with the number 8 to 10 when I define it as non-fatal MI and fatal CHD. So, you already have a negative balance. What happened in the remaining 16 trials? The explanation that was given was that in the second CABG trial that got involved

in the analyses, they subtracted the number of events when the patient was on the I.V. formulation parecoxib. I looked it up and it turned out to be one case. So, that doesn't explain the discrepancy, so the explanation that was given was not satisfactory.

DR. HARRIGAN: Could I have slide D116, please. This is Table 20 in the briefing document; I can't give you the page number. So, as Dr. Furberg points out, this is a table that shows placebo 2,468 and the 4,087 patients from the valdecoxib studies at doses of 20 to 60 mg. Three myocardial infarctions in the valdecoxib treatment group. Now, Table 22 is an illustration, it is a table titled from one of the tables, there are Tables 22 through 27 in the briefing document, which report on the adverse events in the rest of the studies described in that portion of the briefing document. As Dr. Furberg points out, we reported to him earlier today that the myocardial infarctions that he saw in the general surgery study and in the two CABG studies, if they occurred to parecoxib, they were assigned to parecoxib. These are trials in which treatment with parecoxib took place for a certain number of days, and then patients were switched to valdecoxib. If you assigned an event to both treatments, then, of course, you are going through tables until midnight, because they won't add up. You have to assign the event to one treatment or the other, they were appropriately assigned to parecoxib, and so they are not accounted for in the valdecoxib column. A second reason for a difference is that the adverse events in the tables that Dr. Furberg was drawing them from are adjudicated adverse events. So, these are events that were determined according to prespecified

criteria in both of the CABG trials and in the general surgery trial. So, aside from the parecoxib confound, you wouldn't expect those adverse events to add up to adverse events reported in a different way. This is frequently an issue in safety summary documents. There are a number of different ways to record adverse events. You have serious adverse events, you have spontaneous adverse events reported to marketed drugs, you have adverse events recorded in case report forms in clinical trials. By presenting them several different ways, you are sure that you are giving the entire picture, because you don't want to select one picture and be accused of not showing the other two, but you can be guaranteed the columns will not sum up.

DR. WOOD: But parecoxib is the pro-drug for valdecoxib.

DR. HARRIGAN: It is.

DR. WOOD: So, as far as my body knows when it gets parecoxib, it has got valdecoxib.

DR. HARRIGAN: Two points. One is that the events are described in the briefing document as you see, but they are assigned to parecoxib. I don't know if you are suggesting that all treatment groups that receive parecoxib, all patients that receive parecoxib be transformed to valdecoxib.

DR. WOOD: I guess the body transforms it to valdecoxib.

DR. HARRIGAN: It would obscure the data from the effects of parecoxib, which is given by a different formulation. Some people consider that significant, so I think to describe it under parecoxib is

appropriate. To not put it under valdecoxib is appropriate. The data is in the briefing document. It is not hidden. It is not suppressed. It is clearly available in the briefing document. The columns do not add up. We think there are good reasons why they do not add up. There are alternative ways to present safety data. We are happy to, and frequently do, re-run safety data and safety tables with different algorithms and different rules.

DR. FURBERG: The numbers just don't add up.

DR. WOOD: Have you another point, as well?

DR. FURBERG: No.

DR. WOOD: I suggest that we are not going to resolve this this afternoon, so why don't we defer this to Dr. Temple and his staff to resolve. Is that fair, Bob?

DR. TEMPLE: Yes. Curt agreed earlier that he would write down exactly what the concerns are, and we, not me, will follow them up and pin down what is going on.

DR. HARRIGAN: It is important to us that members of this committee and the FDA, and other health agencies worldwide understand that we do not suppress safety data. We report safety data. We report it in a number of different ways. We do not suppress safety data.

DR. FURBERG: But it would be much better if you explained why you did it differently and present the data in one way in one table, another way in another table, the numbers should add up if you

have information from two trials and you have more events than you have in the pooled analysis of 18, that has to be explained. I think there are some numbers that will be hard to explain away.

DR. WOOD: I think we have got it that there is still a bone of contention here. Let's move on to the three questions that we were charged with discussing this afternoon.