meeting in February of 2005 shows a range of COX-2, COX selectivity for various NSAID. The upper, left or the ones on the left are much more COX-2, and the ones on the right are much more COX-1 or less COX-2.

What you can see is that both rofecoxib and etoricoxib are at the far end of the spectrum of increased COX-2, up in the top in the pink or lavender or whatever.

Diclofenac shows much more COX-2 selectivity than naproxen, that's down in the middle purple one for the diclofenac and naproxen is down, the green, in the lower right.

Thus, the similarity in cardiotoxic properties of rofecoxib and etoricoxib are not surprising, nor is the fact that diclofenac is much more cardiotoxic than naproxen.

The next slide just shows the molecular structure and what is common to rofecoxib, on the left, and etoricoxib, on the right, is the sulfone moiety, which is the SO2 CH3. There is a paper suggesting that this particular moiety may be related to the cardiovascular problems that are seen,

particularly with these drugs.

In summary, Merck at some level seems to be trying to have it both ways. Looking at naproxen studies, there is some GI advantage but much smaller than the cardiovascular disadvantage that you see with the drug.

This was the same with the VIGOR study. It showed some, not huge, some gastrointestinal advantage but a four- to fivefold increased risk of heart attacks, not really comparable, though.

Looking at diclofenac studies, there is no cardiovascular difference but no GI advantage as far as confirmed serious gastrointestinal complications. If Vioxx were coming up for approval versus naproxen -- the VIGOR study, which was after approval, but this has been the kind of study that was done before -- would it get approved? The answer is no.

Then, why should the similarly dangerous offspring of Vioxx, etoricoxib, get approved just because its cardiovascular risks are no greater than an older NSAID with known cardiovascular risk, diclofenac, as in the MEDAL study when, like its

parent, Vioxx, it has been previously shown to have increased cardiovascular risk in randomized trials in which it is compared to naproxen?

For etoricoxib, there is no evidence of a benefit in efficacy compared to older NSAID, as the company admits, nor evidence of a benefit in terms of reduced serious GI complications such as perforations, ulcers, and bleeds compared with older NSAID, except possibly some advantage with naproxen.

Thus, in the face of seriously increased cardiovascular risk compared to drugs such as naproxen, how can the approval of etoricoxib and the large numbers of preventable life-threatening cardiovascular reactions be justified?

If you were prescribing etoricoxib to a patient with osteoarthritis, on the basis of what evidence would you inform them that the significantly increased risk of a heart attack or other cardiovascular events with this drug is outweighed by the increased benefits when there is no evidence there are any such benefits unique to etoricoxib as far as increased efficacy or reduced serious gastrointestinal

adverse reactions that even compare to this huge increase in cardiovascular risk?

Since there is no basis for informing your patient of such a favorable risk-benefit ratio, there is no basis for recommending the approval of etoricoxib.

Thousands, probably tens of thousands of patients have already had needless heart attacks because they took one of the marketed or previously marked, two of the three are off the market, COX-2 drugs instead of clearly safe alternatives such as naproxen.

It is time to shut the door on further additions to this dangerous class of COX-2 inhibitor drugs. The idea that there may be certain patients, however unidentifiable they are, who might be benefit from this drug is just not good enough as a basis for its approval.

Such anecdotes often suffice before 1962, when the FDA's legal authority was finally expanded to include the requirement for evidence of effectiveness for randomized control trials.

Only with this kind of information can an accurate assessment of benefits and risks be made. Etoricoxib does not fulfill a "unmet need" as required by the FDA for any identifiable group of patients.

The Merck discussions in their briefing document about "unmet need for treating OA" merely describes how prevalent OA is, we have no reason to think it isn't accurate, and reviews the various treatments.

The company actually admits that for people with GI problems, this is in the submission, the recommendation includes use of a traditional NSAID with a gastroprotective agent, a PPI or a misoprostol or a COX-2 inhibitor. No explanation is given as to why etoricoxib fills specifically an unmet need, other than anecdotes that you have heard and will hear.

In addition to strongly urging your Committee and the FDA to reject Merck's effort to approve etoricoxib in the United States, I urge prompt removal of Arcoxia from the market in the sixty-plus countries where it is causing unacceptable risks to the hundreds of thousand of people using the drug.

Just one other comment. I jotted down some of the notes from the Merck presentation as to why this drug is needed.

"Another option, valuable treatment option."

"Need to expand the number of options."

"Patients want and desire this."

Well, if we had something that was better than what exists, it would be a different thing. You might be able to weigh the benefits and risks. But it isn't any better in terms of efficacy. The whole evolution of the COX-2 slide was in a hope which I had also that they actually would prevent gastrointestinal complications.

Vioxx did slightly, outweighed by the cardiovascular risk; Celebrex does not; and certainly this drug, in comparison with diclofenac, does not. It is time to stop messing around with people's health and doing any more clinical trials with these drugs.

The FDA should clearly stop encouraging any companies -- and that includes Novartis for Prexige®, it includes Merck, or any other companies -- from doing any more clinical trials on these drugs. They

are fatally flawed drugs.

Thank you.

CHAIRMAN TURK: Thank you very much.

MS. CLIFFORD: Our next speaker is Patience White

DR. WHITE: Good afternoon, Mr. Chairman and members of the Committee. My name is Dr. Patience White.

It is a privilege to appear before you this afternoon on my capacity as chief public health officer of the Arthritis Foundation, the nation's leading voluntary health agency working on behalf of the 46 million Americans with doctor-diagnosed arthritis. In addition to my responsibilities with the Arthritis Foundation, I am a practicing rheumatologist in Washington, D.C.

I would like to begin by confirming that I do not have any direct financial ties or other relationship with the Applicant company, Merck. The Arthritis Foundation, however, accepts charitable contributions from a wide variety of entities.

For nearly six decades, the Arthritis

Foundation has been representing the interests of people with arthritis. Our volunteers and staff coordinate to fund research, deliver disease-prevention programs, and advocate for quality healthcare. We welcome the opportunity to appear before this Panel and appreciate your role in protecting the health of Americans with arthritis.

While the Arthritis Foundation is not in a position to comment specifically on the Applicant's supporting data on Arcoxia itself, we support all reasonable efforts to help ensure that the widest range of safe and effective therapies are available to people who suffer from arthritis. We want to emphasize the needs of patients with arthritis.

Osteoarthritis affects at least 21 million Americans. We have no treatments that alter the progression of this disease other than physical modalities such as exercise and weight loss. As a result, patients face progressive pain and disability for the remainder of their lives.

Some can be helped with major surgical procedures such as joint replacements, but the

majority must turn to whatever symptomatic medications are available for control of their pain.

We want to draw attention to the risk of untreated arthritis. The loss of joint function is a leading cause of reduced cardiovascular fitness, second only to the lack of exercise.

The reduced activity leads to muscle weakness and increase in falls and bone fractures. The inability to engage in exercise likely contributes to the progression of degenerative diseases such as Alzheimer's disease. Thus, maintaining mobility and physical activity becomes an increasing priority for the aging American population.

The careful use of nonsteroidal antiinflammatory drugs can help achieve this goal. In addition, we believe that the risk and benefits of NSAID may be different for patients with arthritis compared to the population as a whole.

The systemic inflammation associated with diseases such as rheumatoid arthritis appears to promote cardiovascular disease. We do not know whether NSAID have a positive or a negative effect on

this particular disease mechanism.

For these reasons, the Arthritis Foundation favors the development of the widest possible range of choices among antiinflammatory medications. Please keep in mind that individual patients respond differently to the range of NSAID.

Therefore, we support all reasonable efforts to add new NSAID to the list of drugs available for patients with arthritis. We believe there must be a balanced approach involving the patient and his or her physician and weighing the benefits and risks associated with this new drug.

In summary, our concerns today center on patient access and consumer-driven perspectives that are relevant to the Committee's work. The Arthritis Foundation urges the Committee to consider the underlying risk of osteoarthritis, the importance of relieving pain in this disease, and the limited options currently available to people suffering from this disease.

We believe patients must have the widest possible range of therapeutic options to appropriately

manage the pain and disability of the disease. We are convinced that a sound regulatory process combined with an informed healthcare can optimize the effectiveness of all approved therapies. The Arthritis Foundation remains committed to working with the FDA to this end.

Thank you again for this opportunity to represent the Arthritis Foundation in these proceedings.

CHAIRMAN TURK: Thank you very much.

I want to thank all of the speakers who addressed us at this open forum. If there is anyone else, we have a few minutes, who would like to make any comments from the public, we would be happy to hear those at this particular point in time.

(No verbal response.)

CHAIRMAN TURK: Okay. In that case, what we will do now is take a break for lunch, approximately 45 minutes. We will be back here at 1:15. Thank you all for your patience and for participating to this point.

(At the hour of 12:30 p.m. the luncheon

recess was taken, the proceedings to be resumed this same date and place at 1:15 p.m.)

* * *

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:15 P.M.)

CHAIRMAN TURK: This morning we had presentations by a number of individuals from the sponsor, from the Food and Drug Administration, as well as the open hearing.

What we would like to do in the next section is to have questions from the Panel to any of the speakers that we heard from this morning. We have already had some questions and I had tried to encourage us to keep those for clarification questions. Now we can open this up to some of the questions that are more specific or more detailed about aspects of the material that was presented.

Let's see, first, we have Dr. Cannon.

QUESTIONS FROM THE COMMITTEE

DR. R. CANNON: This is a question for Dr. Curtis. If Dr. Chris (sic) Cannon is here, he may want to respond. I should point out that Dr. Chris (sic) Cannon and I are not related. We might ask Dr. Cannon, who is from Utah, when he gets back home to check it out. It might be we're closer than we

realize.

(General laughter.)

DR. R. CANNON: My question relates to the interaction of cardiovascular risk factors at baseline with the outcomes in the MEDAL Program. Specifically, I know that about a third or so of patients or subjects entering the MEDAL Program were felt to be dyslipidemic. Some of those were on statin therapy.

I take this from the Lancet paper published in November. About half the subjects were considered to be hypertensive at entry into the study, and many of them were on medications.

My question is, was there any interaction of medical management of statin treatment for the dyslipidemic patients or antihypertensive therapy with the outcomes?

Or, another way of saying that, were the patients who were treated for their risk factors more likely to have a better outcome in either treatment group than those who were not treated?

Is there any evidence of a protective effect of current medical management or risk factors on

outcomes with treatment of either agent in the MEDAL Program? Any signal that there might be benefit of medical management or a protective effect of medical management?

DR. CURTIS: Can I have Slide 1352, please?

(Staff complies.)

DR. CURTIS: Dr. Cannon, to get to your question, this is a summary of the subgroups of demographics and risk factors based on baseline risk factors for patients in the entire MEDAL Program. This is everything, OA, RA, 60 and 90 milligrams, the primary assessment.

Again, just to get to your answer, again, I presented the relative risks for some of these subgroups in the core presentation, including sort of basic baseline demographics, as well as primary risk factors.

You can see that by risk factor, as you get older, your CV rates go up. To your point, patients with a history of dyslipidemia had higher absolute rates than patients without. The relative risks here, all these subgroups had negative treatment by subgroup

interactions. Now, to answer your question, I think you're asking how these patients were managed, for example?

DR. R. CANNON: The specific question, for those patients who were treated for their risk factor, for example, I think I recall from the Lancet paper about 15 percent or so of patients were on statin therapy. Certainly, there were patients on various antihypertensive therapies.

Were patients who, presumably, were appropriately treated for their risk factor? I acknowledge that the risk factors increase the risk of cardiovascular events in either treatment group. But is there any signal or any hope that medical management might reduce that risk to either agent?

DR. CURTIS: Specifically, with regard to analysis from this dataset, we aggressively asked for current clinical guidelines, had an investigator manage all primary risk factors, hypertension and dyslipidemia. But in terms of actually looking at patients, in terms of a response on what their CV events, we don't have specific analyses to look at

that.

If Dr. Cannon would like to add anything--?

DR. G. CANNON: That's a good point. We always look to large trials to see could we see the expected benefit of aspirin or statin therapy. There were data published at the American College of Cardiology in a large observational registry, the REACH registry.

In that analysis, being on aspirin or being on statins were protective in an observational fashion as we would have seen in trials. We have not done observational analyses here to say would it be beneficial to take aspirin to reduce risk or to take statins and focused really for this look at the coxib on the randomized data.

I think your point is well taken, that we need to manage the risk. As Sean just said, within the trial program Loren developed a risk factor sheet, that we faxed multiple times to each investigator, to make sure appropriate patients were on proton-pump inhibitors, and ended up with about 40 percent on them.

We did the same aggressively for aspirin to make sure that anyone with atherosclerotic disease or diabetes was put on low-dose aspirin as per guidelines.

We tried to adopt the guidelines and proactively address them to make sure that these were as well-treated guidelines as we could. I guess the same for blood pressure as well.

CHAIRMAN TURK: What I would like to do is see if there are questions that are related to this topic, so we can try and keep things together, if there are such. If not, we will move on to Dr. Levin.

DR. FELSON: I'm not exactly sure what the topic is, but if it's cardiovascular complication issues, Merck said that they did have some data on baseline demographics and comorbidity characteristics of patients who were enrolled in MEDAL compared to the base population. I think that would be helpful for our deliberations, if that were okay to be presented.

DR. CURTIS: On Slide 903, I can characterize in a little more detail the patient baseline characteristics for the pooled MEDAL

population here. Now, as I mentioned, the inclusion criteria were patients at least 50 years old with a diagnosis of osteoarthritis or rheumatoid arthritis.

From a cardiovascular perspective, we reviewed the exclusion criteria around patients with acute coronary events within the previous six months and patients with uncontrolled hypertension or uncontrolled CHF were also excluded on enrollment.

This is a summary of the patient baseline characteristics we get as a result of those inclusion criteria, obviously well balanced between the two treatment groups.

Almost half the patients had a physician diagnosis of hypertension at baseline. In terms of patients with documented symptomatic atherosclerotic cardiovascular disease, approximately 12 percent of patients had that on entry in the study. If you add that plus at least two primary cardiovascular or at least two primary risk factors, you see that that number comes up to about 40 percent of the patients.

This represents, again, based on the size of the study, the geographic distribution within the

context of the inclusion criteria, we feel this represents a reasonable clinical cohort that would be typically managed with an NSAID.

CHAIRMAN TURK: Let me follow up on that, if I might. In the trial of this type you're referring a patient, if you're the physician, to a trial for a medication that has the potential to have a cardiothrombotic effect.

Would that not mean that I would select or preselect certain types of patients that I wouldn't send into this particular trial, and would the implication of that be that any results you see in this trial would be an underestimate of what you might see occurring in the real corticoid world?

DR. CURTIS: The inclusion/exclusion criteria were in line with NSAID labels. Again, this was a worldwide study. We had, as you know, the NSAID and COX-2 inhibitor labels in Europe exclude patients to be treated with ischemic heart disease, within the constraints of running a clinical trial, we feel. I can summarize it on Slide 604, some of the major exclusion criteria.

You know, obviously there are limitations to any clinical trial. But, to the degree we could based on current guidelines for that with NSAID and the degree to which obviously we could have investigators justify treating a patient chronically with an NSAID, we feel these represent a reasonable inclusion an exclusion criteria. They are listed here. The major ones, I've discussed them.

Patients with uncontrolled hypertension were excluded; Class III or IV, CHF; and, as I mentioned, any patient with an acute cerebrovascular or coronary event within the last six months.

That being said, this is we feel as real-world, if you will, or representative of a patient population that would be getting these types of therapies, but there are limitations to any clinical trial.

CHAIRMAN TURK: Thank you.

Dr. Davis.

DR. DAVIS: Along those lines in terms of generalizability, you excluded morbid obesity, but do you have baseline BMIs for the two groups?

DR. CURTIS: Yes, if you will give me one moment. I think that the baseline BMI was approximately 30. If you give me a moment, I will confirm that.

(Pause in the proceedings.)

DR. CURTIS: These were patients, again, the majority were female, predominantly the average was 65. Typically, in these studies, we've seen BMIs right around 30 to 31. I will confirm that with you, sir.

CHAIRMAN TURK: If I'm asking people out of turn, it's because I'm trying to keep items, questions, together.

Dr. Morris.

DR. MORRIS: I'm trying to reconcile some of the relative risk figures. In the presentations by FDA, Dr. Shibuya and Dr. Graham used a relative risk of 2.72 for the etoricoxib/naproxen comparison. On your Slide Number 22, you have a relative risk of "1.7." I know it's a difference in endpoints, but they seem to be fairly similar endpoints. Can you describe the differences, and explain why you chose

your particular thrombotic cardiovascular events?

DR. CURTIS: Sure. When we started the development programs for the COX-2 inhibitors and developed an adjudication procedure, we wanted to be as inclusive as possible of all potential events, and therefore we chose to use a confirmed thrombotic endpoint that had as many events as possible.

The major differences between our endpoint and the APTC endpoint is the fact that the APTC endpoint is MI, stroke, and vascular death. The confirmed thrombotic event includes additional events, the two most common would be TIAs and unstable angina.

Those are what we consider thrombotic type of events in the sort of thrombotic milieu but don't represent hard endpoints, if you will, or as hard endpoints as the strokes and MIs because they require some clinical judgment.

DR. MORRIS: Just as a followup question, in the VIGOR trial when we talk about the events that occurred and a relative risk of 2.37 for all cardiovascular events, is that measure closer to your thrombotic CV event, or is that closer to the ATPC

endpoint?

DR. CURTIS: I'm sorry, which endpoint?

DR. MORRIS: For the VIGOR trial.

DR. CURTIS: Okay. The VIGOR trial would have used the same endpoint that we're using, the confirmed thrombotic events.

DR. MORRIS: Okay. The VIGOR trial and the one that you're using would be the same endpoint, and the relative risk is different? I think the relative risk that the FDA presented was 2.37, and this is Dr. Hertz's presentation.

DR. CURTIS: Okay.

DR. MORRIS: Yours is still 1.70. That's the same outcome measure?

DR. CURTIS: That's correct, that's the confirmed thrombotic endpoint. That's a composite endpoint, I'll just remind you, on Slide 1328.

If you could please show 1328?

(Staff complies.)

DR. CURTIS: These are actual results. But if you focus on the left-hand column, these are all the events that are included in the confirmed

thrombotic endpoint. These are the different cardiac events, cerebrovascular events, peripheral vascular events.

These are what are not included in the confirmed thrombotic endpoint, because these are vascular deaths which then are included in the APTC. These are the three categories for the composite endpoint. Yes, it would be similar between our development program and the VIGOR trial.

*DR. G. CANNON: There were questions about in the event rates of what would an outside reference point be. In Dr. Nissen and Topol's and Mukherjee's original editorial, they did just such an analysis to see what would be the expected MI rate in a normal population, and so they analyzed the data from trials and found it to be 0.52 expected rate of MI per year.

You just saw -- now if you want to put the slide up -- it's pretty similar of exactly that. It's quite different than the two percent rate that was obtained from Framingham risk in older men only, recalling that this is three-quarter women who have arthritis.

I think in terms of generalizability, the original "JAMA" editorial that called attention to this came up with a rate of .52 per year of MI, which is spot on with what we observe in this large real-world trial.

CHAIRMAN TURK: Dr. Felson.

DR. FELSON: Just to follow on to that, I mean, those are very age-specific. You would have to match for every year of age in the numbers, because the cardiovascular rates, the thrombotic rates go up very rapidly with age. They double every eight years of additional age.

CHAIRMAN TURK: Dr. Stine.

DR. STINE: Hi. I just had a simple question. You don't have to go Slide 14,000, just number 22.

(General laughter.)

CHAIRMAN TURK: They happen to have 14,000.

DR. STINE: I think they probably do.

CHAIRMAN TURK: I always get concerned when we start making conclusions from meta-analyses. This is kind of a meta-analyses; right? Those three

confidence intervals I see there don't come from a randomized study, right, not one randomized study?

DR. CURTIS: That's correct. These are data that came from the 18 studies.

DR. STINE: Right.

DR. CURTIS: It would be considered, I guess, a "pooled analysis," if you will. It was controlled for disease; it was stratified by disease.

DR. STINE: Right. But, for example, the duration of these studies differ?

DR. CURTIS: The duration? Yes.

DR. STINE: For example, versus naproxen is a year, maybe even longer, whereas versus the other ones were shorter?

DR. CURTIS: Yes. Well, the placebos certainly were shorter. The maximum duration of treatment of any placebo comparison would have been 12 weeks.

DR. STINE: Would that not have some effect on making these comparisons?

DR. CURTIS: Well, the reason we pooled this to show these result?

DR. STINE: No, not why you pooled within each row but rather why you compare the rows. I mean, this plot is definitely there to make me compare these different results, but I'm not seeing all the differences that lead to those results.

What's implicit behind this is I'm thinking this is a randomized study, but in fact it's not. The people that are in the first row were observed for a different length of time than the patient in the second row and then the people in the third row.

I don't think that is endemic to this analysis so much as any meta-analysis has that problem with mixtures of populations. We heard about that with the PPI comments earlier. How am I to make a comparison here when, in fact, those really aren't comparable numbers?

DR. G. CANNON: The comparisons actually are three different comparisons and so these are randomized data. The entire program is randomized data.

DR. STINE: Those are not randomized to the different, within one study?

DR. G. CANNON: No. The comparisons to be compared are etoricoxib versus placebo, and so it might be better to conceive of this as three separate slides. There are no rates, you will see, of event rates to say what's the difference in this or that group because that is a nonrandomized comparison statement.

DR. STINE: Right, but they are shown on a common scale with a vertical line that connects them.

DR. G. CANNON: The comparison is to look at is etoricoxib as compared with either a placebo, the non-naproxen or naproxen. That's the pairwise comparison all randomized.

DR. STINE: Okay.

DR. G. CANNON: One shouldn't compare to say, is naproxen better than non-naproxen on the basis of this, because that would be an observational, nonrandomized comparison.

DR. STINE: Good.

DR. G. CANNON: I think we agree.

DR. STINE: Okay.

CHAIRMAN TURK: Dr. Saag.

DR. SAAG: Dr. Egilman and others raised some questions about adverse event adjudication. I would like to hear a little bit more about that, specifically as it pertains to CHF and atrial fibrillation; the timing of the adjudication; how the scale was determined, pre-hoc and post-hoc.

I would also be interested in hearing from the FDA based on some of the comments that were shown from Dr. Schiffenbauer's review and whether the FDA had concerns about that issue as well.

DR. CURTIS: Okay, sure. Well, I'd like to talk about the adjudication of the congestive heart failure, since that was your specific question.

Slide 656.

(Staff complies.)

DR. CURTIS: Just to be clear, the data from the MEDAL program for congestive heart failure were adjudicated. This came out of a request from the Data Safety Monitoring Board, who had been employed from the beginning of the study.

At one of their meetings they asked us, and this was near the end of the trial, they asked the

steering committee to implement a process to adjudicate congestive heart failure. We and the steering committee of course took on this recommendation by the DSMB and their specific request was to adjudicate cases resulting in hospitalization.

At that point we were well into the program. Of course, the sponsor, the adjudication committee's investigator's report still blinded completely the study therapy at this point.

We wanted to just go ahead and adjudicate based on that recommendation. We implemented the following process. We looked at all eligible prespecified congestive heart failure terms in the reporting dictionary. I can go through all those terms, if you would like.

We determined that we would adjudicate in any blinded fashion any serious adverse event report of congestive heart failure for one of those terms occurring on study therapy or within 28 days after the last dose of study therapy in all three of the MEDAL Program trials.

We implemented this adjudication procedure.

It went to all the investigators and set up prespecified adjudication criteria with the Cardiology Adjudication Committee.

As part of that, and again in a completely blinded fashion, went in and sent in all this supporting information to the adjudication committee. They reviewed the data, as they had been doing throughout, for thrombotic events as well as for upper- and lower-GI events and made independent adjudication of those data.

On the next slide, on 757, are the general criteria that were used -- if you could go to 757, please -- showing the criteria for adjudication. Again, these were all potential cases and those specifically resulting in hospitalization or emergency room visit. The DSMB made it very clear they did not ask to see events of heart failure that did not meet these criteria.

They had specified adjudication criteria based on these types of criteria: based on symptoms or signs of heart failure, any lab data or imaging data they had, as well as whether the treatment for that

case was consistent with treatment of heart failure.

On Slide 658, please, is the general diagnostic criteria employed by the adjudication committee.

Now, there were limitations to some degree. The EDGE study had been finished at that time, but this did not preclude our ability to go back and, again in a blinded fashion, include all those events as well; so, they were included.

There were a total of I think 124 cases. They were adjudicated in equal portion, 82 percent were confirmed on etoricoxib and 83 percent were confirmed on diclofenac.

There were equal adjudication rates between the two treatment groups, and that's the case for our thrombotic event. We have never ever seen a differential confirmation rate between treatment groups in these procedures.

DR. HERTZ: Instead of rushing through Dr. Schiffenbauer's review trying to guess what you were referring to guess what you were referring to, so I think rather I'll ask.

DR. SAAG: There were a couple of quotes raised from his review that pointed at some potential concerns about the detection of various cardiovascular endpoints. I was wondering if you could comment on what those issues were?

DR. HERTZ: I saw one comment where there were a few cases that were recorded as insufficient that could have been potential cases, that type of thing.

Well, what we did for our current review was we actually had a separate Medical Officer, Dr. Gibbs, assigned to take a look at the adjudication process so that we could be sure that the data we were looking at was the appropriate data.

Dr. Gibbs did a review of the cases. He looked to see if there were any differences in the number of type of cases that were adjudicated positive or negative for the cardiovascular and the GI events. He did not find any irregularities or concerns that would make us doubt that we had the right cases to look at.

CHAIRMAN TURK: Dr. Levin, you've been

waiting patiently. Sorry.

DR. LEVIN: No, it's perfectly all right. It makes sense to stay on one topic.

I guess this is a question for division staff. Given the fact that Merck made a presentation on this drug at the February 2005 hearing and in the transcript, and I was there as well, there was a vigorous discussions about the appropriateness of the comparator drug, diclofenac, could you tell me subsequent to that meeting were there conversations with Merck about that issue? If there were, how would you characterize those discussions?

DR. HERTZ: I can't say that we had discussions after the 2005 event, but as part of the review I did go back and check our records. We did on at least four occasions while the studies were being designed comment that we were concerned about the design with only one comparator, and that one comparator being diclofenac, because we were concerned about just this kind of discussion at this point, sort of where we are today.

DR. LEVIN: I guess we know how Merck

responded.

CHAIRMAN TURK: While we have the FDA, I thought I might ask a question of you. In Dr. Graham's presentation, he raised a concern about the 2006 document that was put out by the FDA about the appropriateness of NSAID and the dilemmas that they all have. That sounds somewhat different. I would be interested in your perspective of his comment that "You got it wrong," and the FDA perspective.

DR. MEYER: I'll try to answer that. I think the document in question was crafted in 2005 and partly informed by the Advisory Committee meeting that took place on the issue of COX-2 and NSAID-related cardiovascular events in February of 2005.

At that meeting Dr. Graham expressed the opinion that Naprosyn® did have an increased cardiovascular risk. Although there has been new meta-analyses available, it's not entirely clear to us sitting here today what the basis of the change he has had with regard to the Naprosyn risk, what the basis of that is.

That's partly because we've not had formal

conversations with him other than hearing about it today in terms of what has changed his mind about the risks specifically of naproxen.

CHAIRMAN TURK: You're saying you don't think you got it wrong until you see more data?

DR. MEYER: I don't think we got it wrong in 2005. Whether it needs to be rethought I think is something that is sort of an ongoing question and I would be happy to, you know, reconsider the general conclusions of that document over time as more data accumulates.

CHAIRMAN TURK: Dr. Levin.

DR. LEVIN: As somebody who was part of that committee, I would take issue. I would say you did get it wrong. I don't think it was the intent of those Committee votes that we have a generic black-box warning that didn't at least address what was known at that point. I think that was a disappointment to me, and I think it was a disappointment to other members of that committee that I've spoken with about it. I'm not sure that you got it right then.

DR. MEYER: You're certainly welcome to your

opinion, and I believe I'm welcome to mine as well.

CHAIRMAN TURK: Dr. Graham, do you want to respond?

DR. GRAHAM: Yeah, I would just like to say a couple of things. One, in the 2005 presentation the evidence that I was talking about for naproxen was based on a study that I was a senior author on. In that study, we found an increased risk with naproxen. It was an observational study done at Kaiser Permanente; it wasn't a meta-analysis.

What I've presented today is basically the world's literature on both randomized clinical trials and published observational studies, and those both agree that there is no increased risk of cardiovascular outcomes with naproxen.

Now, I would also like to point the Committee to, if you look at what was presented, some of the slides were actually presented today in Dr. Wolfe's talk, abstracts from was discussed at that 2005 meeting.

When you look at that data, the data that was available there did not say that naproxen has an

increased risk. It may not have reached the level of certitude that people in the reviewing divisions like to insist upon, a "P" less than .05, before they will believe that there isn't a problem, which is just looking at things all the way wrong.

But, if you go back and you look at the slides that Dr. Wolfe presented, the data there suggested that naproxen did not increase the risk. It just didn't maybe reach the level of certitude that they would like to see. If we pull the transcript out, I think you will see that there is differential risk.

DR. MEYER: David, may I ask, just in followup to that, are you saying that for a conclusion that there is no safety risk, that we would be in error to want good, definitive .05 type data? That seems to be the opposite of what you've said in the past.

DR. GRAHAM: Well, there's two different ways of looking at this. We should talk more internally so we don't have to do it over microphones, but I'd say a couple of things.

One, if we look back at the rofecoxib program, there were signals left and right of increased cardiovascular risk at lower doses and higher doses. It's there in the medical officers review. Anybody in the world who wants it can go to the FDA website and see it.

What she says in there is that we don't have complete certainty that there is an increased risk, and so FDA's default therefore is to say, "Well, there is no risk."

If you look at the label when rofecoxib first came on the market, there is no mention of cardiovascular disease there. That's because FDA uses a "P" value. When a drug comes for approval, it says, "The drug doesn't work, and you've got to show me that it does." The "P" has to be less than .05 and then they will say, "Okay, we believe that the drug works."

For safety, it is just reversed. They assume that the drug is safe, and unless you can show me "P" less than .05 that it's not safe, they go ahead and they assume it's safe. That's what I'm saying is a misuse of "P" values and statistics to the way FDA

approaches safety.

What I would recommend for safety is that you establish a predefined threshold that you have to have the risk be below. You can design and power your clinical trials in that fashion to assure.

Let's say, for a COX-2 inhibitor you say, "Well, I'm willing to tolerate a 10 percent increase in relative risk of myocardial infarction," then you can power the study to exclude the possibility that the risk is greater than that.

That's not how FDA does it. FDA looks at the lower bound of the confidence interval and says, "The point estimate could be 1.3, but if the lower bound of the confidence interval goes below one, and the "P" is .07 and .08, it doesn't show up in the label."

CHAIRMAN TURK: I don't think the intent of this meeting is to go into these. I'm going to let the FDA have the last response, but I just want to say that I don't think we want to spend a lot of time on internally how the FDA is going to choose to look at these.

DR. MEYER: No, and I agree. I just wanted to be clear that what I heard as one of the points that Dr. Graham made about the FDA's being in error in the 2005 document was about whether Naprosyn is safe.

Given what he has just said, I would think we would want definitive data to inform a conclusion that it's safe and that absent that, that our decision in 2005 was absent those data, that the safest thing was to conclude that Naprosyn probably did have a cardiovascular risk, particularly since there were some data available at that time including the preliminary data from a controlled trial using Naprosyn as a comparator that did show evidence of a cardiovascular risk.

CHAIRMAN TURK: Dr. Jenkins, last word.

DR. JENKINS: I think it's also important to say that I think that Dr. Graham, his characterization of how we look at safety data is simply false. He should know that.

We don't just look at "P" values when we're looking at safety data. He may be able to pull out one example from where a reviewer made the comment

that was made in review, but there are many, many examples of where we make safety decisions and take safety-related actions based on data that don't reach a "P" value.

It is not a correct statement to say that we just look at "P" values for safety data; we look at the data. We make our best informed judgment about what the regulatory action should be.

I just think it's important for the Committee and everyone to know that that is simply a false characterization of how we look at safety information.

CHAIRMAN TURK: Thank you.

I'm going to switch the topic now. Dr. Pasricha has been waiting for a while.

DR. PASRICHA: Thank you.

This is a question about GI events. I would like to know a little bit more about the post-event clinical care of these patients. The patients who developed a complicated event, were they taken off the drug, or what happened? Did they have a followup endoscopy? Do you have any information on death rates

from complicated GI events?

DR. G. CANNON: The management of patients who developed an upper-GI event was largely left up to the investigator as per their current clinical practice. I can tell you the vast majority of patients were discontinued from the trial, but it was not an absolute forced protocol mandated approach.

Followup would have been, again, as per standard routine practice, depending on the severity of the event -- obviously patients with medically the more serious events such as the perforations and obstructions would have obviously been hospitalized and managed appropriately.

I can tell you that there were only three fatal upper-GI events, one on etoricoxib and two on diclofenac. But in general, the management of those patients was as per clinical guidelines with, presumably, appropriate curative therapy.

CHAIRMAN TURK: Dr. Hennessy.

DR. HENNESSY: Thank you.

This is a question for the sponsor. A number of people have suggested that with rofecoxib

patients who didn't tolerate other nonsteroidal, antiinflammatory drugs or were at high risk of GI bleed may have had a net beneficial benefit-risk balance with the drug.

I'm not sure whether I buy that or not. But if that's true, people have said that one of the reasons that the drug got in so much trouble was that it was mass marketed rather than marketed to the individuals who were most likely to benefit from it.

Given that etoricoxib looks like it has about the same cardiovascular risk as diclofenac, I'm wondering why or whether any thought was given to marketing it with a much more restrictive risk management plan to try to ensure that only the patients who are most likely to benefit from the drug received it?

DR. G. CANNON: We feel we have articulated and communicated the core elements of a risk management plan, risk assessment through extensive clinical trials data, and risk communication through the efforts and items that I articulated -- including of course the core, core content of risk communication

is the product label.

Therefore, with those core elements of a risk management plan in place, along with the additional efforts around the physician education and physician awareness we talked about, we feel that forms the basis for a comprehensive risk management plan. But as I also mentioned, we look forward to working with the Agency to make sure that those efforts would meet their needs.

CHAIRMAN TURK: While we have you up there talking about risks, I'm wondering, I think it was Dr. Felson who mentioned the concept of "number needed to harm" and we've heard from the FDA about relative risk.

I wondered if you calculated out the number needed, let's do it both ways, to treat to protect from one uncomplicated GI event and the flip side is the number needed to harm one individual with a cardiothrombotic effect?

DR. CURTIS: Well, I would like to just speak to that, show sort of the benefit and risk, if you will, of etoricoxib compared to naproxen, for

example. I think as the data have shown it's a complex question because as you saw, based on our datasets, it depends on which NSAID you're comparing yourself to.

We do believe that naproxen has a lower thrombotic cardiovascular risk than the other NSAID. Our data, in fact, are quite consistent with that. When you look at the benefit/risk, if you will -- Slide 275, please -- it depends a bit on which comparator you're talking about. Let me show you what I mean by this.

This is a comparator, again, just to pictorially put the MEDAL results a bit in the context of what you're talking about. Here we have thrombotic cardiovascular events for etoricoxib versus diclofenac overall. As we showed in the per-protocol primary analysis, the relative risk was 0.95; the rates were the same.

Now, on overall GI events, you see the rates were actually quite low. These event rates, by the way, in the MEDAL were 60 percent lower than have been observed in other recent clinical trials.

Nonetheless, there is a relative risk/benefit for etoricoxib here.

Back to the thrombotic side, you see that whether or not one was on aspirin or not, obviously the addition of aspirin, frankly, as probably a surrogate of underlying cardiovascular risk on an absolute scale increases your rate, but the relative risk here is maintained.

On the GI side, again, for overall upper-GI events, the overall benefit observed was, as we talked about, seen in patients without aspirin as well as in regular aspirin use.

Now, this equation changes a little bit when you compare yourself to naproxen. I would like to show sort of the same slide on the -- next slide, please -- similar rate of thrombotic events and upper-GI events when you compare etoricoxib to naproxen.

Confirmed thrombotic events, we've talked extensively about the relative risk of 1.4 and naproxen being lower. But on the GI side, to put this relative risk in absolutely terms, you see that the

event rates were higher overall on GI events for naproxen as compared to thrombotic events, and this relative risk favors etoricoxib.

In terms of generating NNTs, I think it really boils down to which NSAID comparator you're talking about. Because we see that there are different relative risks and advantages, depending on the NSAID comparator. Really, that's what makes this such a difficult therapeutic area.

We talked about this, the benefits and risks we feel need to be weighed on an individual patient basis based on a thorough understanding of the compound.

That's why we think the MEDAL Program provides, in comparison to diclofenac, a wealth of information to help this on an individual patient basis. NNTs do depend on the absolute rate of events, and therefore I feel that that should be a discussions based on an individual patient basis.

CHAIRMAN TURK: As you said, you can look at NNTs across any one of these. Do you actually have data on NNTs for all these comparators?

DR. CURTIS: We have not generated NNTs for all these comparators, no. Again, the reason for it is this is an individual patient decision, weighing the risk and benefits. That equation will change and be different among different patients.

CHAIRMAN TURK: Okay. What you're saying is you're sticking with relative risk and are staying away from absolute risk?

DR. CURTIS: What I'm saying is that the NNTs, in my opinion, don't allow one to make decisions on an individual patient basis.

CHAIRMAN TURK: Okay. Thank you.

Dr. Crawford.

DR. CRAWFORD: Thank you. I'm not quite sure, Dr. Curtis, that I heard an answer to Dr. Hennessy's question, so I would like to probe that a little bit more. As a request, would you please ask for Slide 62 to be projected again?

(Staff complies.)

DR. CRAWFORD: Thank you. I did hear what you were just saying with respect to, in your opinion, this is a comprehensive summary of the core beyond

labeling of if the product were approved at the post-approval activities in risk management.

I was struck with all of the wonderful slides you presented for us at how we've only seen one of a proposed risk management plan beyond labeling. I would like to ask a little bit more specifically, because some of these are just standard boilerplate, if you or anyone from the sponsor would comment about specifically what would educational programs encompass?

Part of it addresses Dr. Hennessy's comment on, would there be efforts to limit the use? We are all very familiar with the problems that occurred with the products that were voluntarily withdrawn with the unlabeled indications, the widespread, and many would consider them, inappropriate use.

I've seen nothing proposed from the sponsor that would be part of a risk management plan looking at that. I don't see anything with respect to studies about duration, or was there any consideration of a formal Phase IV study? Please talk with us, if you would, a little bit more specifically about proposed

post-approval activities.

DR. CURTIS: Sure. Let me talk a bit more about the physician education component of this. What we're talking about from a content perspective is education really fundamentally based on the content of the label, that any material related to educating physicians really, in our view, will responsibly communicate both the benefits and the risks for the compound.

By "risks," we're talking about what we view as NSAID-type class risks: thrombotic risk, renovascular risk, and GI risk. On the benefit side, of course, the fact is that these drugs do work in arthritis and this compound is efficacious.

From a content perspective, we're fundamentally talking about extensive efforts to educate patients and physicians about that content.

Now, from a methodology perspective, there are numerous channels and numerous ways to communicate this information, ranging from obviously a range of peer-reviewed publications, peer-to-peer educational efforts. We have a whole range of activities that

could be utilized.

Now, in terms of drug utilization, I'm going to ask Dr. Watson to speak to that about those aspects of the risk communication.

DR. WATSON: Thank you. Doug Watson from the Department of Epidemiology, Merck Research Labs. With respect to drug utilization studies, we've done these kinds of studies before. The existence of large, medical care databases and insurance claims databases allow us to look at large numbers of people who use our products.

Depending of course on the uptake of etoricoxib and the numbers that are attained, we can at some point in the near future after approval look at these kinds of databases to understand: who is getting the drug, for what indication, at what dose, how that dose is managed over time, how long patients stay on it.

We can even look at what was their history of NSAID usage prior to receiving etoricoxib. We think that these kinds of studies will be immensely helpful in understanding who gets the product, how

it's used by physicians. We will also be very informative with regard to our education efforts so that we can, you know, focus our efforts where it's most needed.

Thank you.

CHAIRMAN TURK: Dr. Levine.

DR. LEVINE: Thank you. Just before I ask my question, I wanted to mention Dr. Turk brought up the question about the possible prevention and uncomplicated event, gastrointestinal event.

I thought I would mention the editorial that followed Dr. Laine's article in February 2004 about Drs. Drenth and Verheugt from the Netherlands and Radboud University.

They made the statement, the following, that "It would be necessary to treat 259 patients with Arcoxia to prevent one uncomplicated gastrointestinal event in one patient." They made the comment that "Although not statistically significant," they said, "the effect is not large and might not be clinically relevant."

If the sponsor agrees that that number is

correct sort of in answer to that -- you're posing the question, ask Dr. Graham or someone what somebody statistically thinks about that number, whether it is clinically relevant or not, and then I'll ask my question. That's how you get two questions in.

DR. LAINE: Again, in terms of the NNT, we can actually calculate it right here together just by looking at these numbers. You are correct, it depends on the group, but it's 250, 300. It depends on what you're looking at.

In terms of the MEDAL Study versus diclofenac, that would be a reasonable number. Then, if we look at the cardiovascular, because there is zero, NNT is infinite; there's no difference.

If we look at the naproxen, we can see that the GI rates here are about 1.4 up to about 3. You know, basically you can figure the number out. I guess it's something like 60 maybe. Somebody back there can help me out.

It's, let's say, about 60 here. I think that brings up the point that Sean was talking about. Naproxen and diclofenac are different my hypothesis is

because it's the antiplatelet effect.

Diclofenac, although it inhibits COX-1 enough to cause ulcers, probably doesn't have the same antiplatelet effect, would be my hypothesis, and therefore probably isn't as good as naproxen from the cardiovascular point of view, but is perhaps better in terms of GI bleeding from the GI point of view.

We're seeing that here. Here we're seeing a difference, let's say, an NNT of about 60 in terms of cardiovascular. Just looking at these numbers, we can see it's about, let's say, .8 versus 1.4, 1 over .6, that's an NNH of about 200, let's say. Again, I'm doing this roughly. I'm doing it in my head based on this. Just these slides that are being shown, we can actually look at that.

Again, the NNT is very small (sic) for diclofenac versus etoricoxib or etoricoxib versus naproxen -- I'm sorry, it's very large and it's much smaller for naproxen. Then, in terms of the cardiovascular, obviously there is an NNT that you can calculate here, but basically there isn't one verus diclofenac for etoricoxib, if that answers the

question.

CHAIRMAN TURK: The reason I raised it is because I think it's very helpful for us to look at that kind of information. When you're looking at relative risk, you're looking at large numbers. When you're looking at NNTs, you look down to the absolute risk.

I think that is a useful way to do it. I was not criticizing you for not doing it but rather saying it would be helpful for you to have a slide that shows us all the NNTs and NNHs with all those different comparators.

Dr. Levine.

DR. LEVINE: My question now goes to relevant risk. I would like the sponsor to look at this as we pass it on to the Chairman, some extra copies.

In the February issue of "Gastroenterology," that wasn't given in our bibliography, there was a very important article entitled, "The Risk of Upper-Gastrointestinal Complications Among Users of Traditional NSAID and Coxibs in the General

Population," and there was also an editorial, followed by authors that you've already mentioned, David Henry and Patricia McGettigan, entitled, "Selective COX-2 Inhibitors: A Promise Unfilled."

My question is about the use of etoricoxib in Europe. They were relatively small numbers. This was a very well-done article which deserved an editorial and it's causing quite a lot of angst. Number one, they had 1,561 cases between 2000 and 2005.

In addition, they looked at the relative risks on patients who had nine different meta-analysis analyzing the data, nine different coxibs and traditional NSAID.

I will give you progressively the increase in the individual NSAID as we go along: ibuprofen; rofecoxib; meloxicam; celexicob; diclofenac; ketoprofen; indomethacin; Naprosyn, naproxen; and etoricoxib, Arcoxia.

The dramatic finding in this finding was that all of the others pretty much had a relative risk of about 5, indomethacin had 7.2, naproxen had 8.1,

and etoricoxib had 12.

Then, when they looked at the low-medium doses and the high-medium doses, it was even more remarkable. All of the low-medium doses for all eight of the NSAID were five or less. Etoricoxib was up at 12, being the most toxic GI for the upper-GI complications.

When they used high doses, again, most of the hem up to ketoprofen in progression were all down in the less than five range. Indomethacin was the highest one in the high dose, followed by etoricoxib, followed by Naprosyn. The actual numbers were 25 on the high dose for relative risk for indomethacin; for Arcoxia, it was about 15, 14; and for naproxen, about 12.

My question is, have you had any reports in from Europe about gastrointestinal toxicity to the relatively small or large numbers that have been reported post-marketing?

DR. WATSON: Hi. Doug Watson, epidemiology again. I apologize, I'm not familiar with that particular paper, and so I don't know the details. I

can tell you that we know that there is evidence of COX-2 inhibitors being channeled to patients at highest risk of GI adverse events.

In observational studies when you start making comparisons across products, you have to be extremely careful that you're not running into a problem that is confounding by indication in that the patients who get COX-2 inhibitors, in this case etoricoxib which is available in Europe, you know, are not in fact those who are most likely to have GI events. It's difficult to control for those kinds of problems in observational studies.

I can speak to some data that we have on GI outcomes with etoricoxib use in the U.K. Let me just find the right slides, and I can give you a little background information as well.

Could I have Slide 2037, please?

(Staff complies.)

DR. WATSON: We have looked at the usage of etoricoxib in the United Kingdom using the GPRD database. In fact, we have identified every patient who has used etoricoxib from the time it was approved

in the U.K. up until June 30, 2006.

What we did was we examined the characteristics of these patients, looked at patterns of prescribing, and also absolute incident rates of AEs including GI AEs.

As I've said, we covered this period. We looked at them in time cohorts defined by their date of first prescription. These are the different calendar time cohorts. Those are related to important events in the history of our understanding of NSAID and coxibs. This study was done as a postmarketing regulatory commitment to the CHMP.

Could I have the next slide please, 2038?

(Staff complies.)

DR. WATSON: Yes, that's correct.

Overall, there were 21,320 new users. These are the demographics which were constant over those time periods: 60 percent female, about 60 years, about 40 percent greater than 65. These are the indications. We looked specifically for these approved indications. If we didn't find any of those in the patient records, then they ended up in this

category.

Then, with respect to the GI outcomes, this would be slide -- I'm sorry, I actually wanted Slide 2049 to begin with.

(Staff complies.)

DR. WATSON: Before I show you the outcomes -- yes, that's correct -- let me just show you this is the baseline medical history for PUB, for PUBs in this population. You see it runs at about 8 to 9 percent, which is pretty, pretty high.

Then, on Slide 2056 is the incidence of GI events during the initial course of therapy. These are in patients without prior disease with an initial dose of 60 milligrams.

You can see to begin with that there are very low absolute numbers of events. These are the rates per thousand patient-years, so this would be about .7 percent per year, .8, .6, and there were none in that last calendar period.

Although we don't have a comparison group here, you can see that these absolute numbers are quite low. It is a high-risk population being

prescribed the drug. In terms of incident new events, these are fairly low, less than 1 percent per year.

DR. LAINE: Just for clarification, you're talking about the same database actually because this is from Garcia Rodriguez* who uses the U.K. GPRD, and those are the data that he showed. Even the authors in this, my memory is, that they actually indicated that there were very few events, and it was early, so these data need to be taken with a big grain of salt shall we say.

CHAIRMAN TURK: Dr. Hertz.

DR. HERTZ: I just wanted to make a clarification or point something out from an earlier response. When we were looking at the data for the comparisons with naproxen for cardiovascular endpoints, those are for the cardiovascular thrombotic events, which are to show less difference between etoricoxib and naproxen in the APTC.

Also, it was looking at the total combined GI events which show, again, not the complicated events, which is what we heard cited in terms of the risk. The number needed to treat that was discussed

from the publication was based on complicated events.

CHAIRMAN TURK: Dr. O'Neil.

DR. O'NEIL: My concern and question is that in the almost blithering amount of data we've been presented and clearly the legions more that you have in your slide bank, we've heard only a very little about the dose of 30 milligrams.

That is I presume, as I look through the slides and tried to make sense of it, because you have only 1,100 patients treated with 30-milligram dose for a not particularly clearly specified time, as I looked through it. You probably have far less data on the outcomes there.

Nevertheless, we were given outcomes with respect to efficacy for the 30-milligram dose. We were also given outcomes with respect to blood pressure changes, but we were not given the thrombotic cardiovascular outcomes nor the GI outcomes for the 30-milligram dose, which is the dose that we are asked to approve as the starting dose. I was wondering if you have that data that you could share with us, please?

DR. CURTIS: The 30-milligram dose experience comes from the development program. On Slide 223, using the pooled, these again are the 18 etoricoxib development program studies, and this is the dataset that I presented that showed the relative risk for etoricoxib at doses pooled.

This is a breakout of those data by dose of etoricoxib. This is rates of overall upper-GI events by dose over the entire treatment period for the development program.

Again, these are relatively rare events and that, frankly, is why we pooled the data to try to get with some sense of precision what the rates are. Nonetheless, I completely agree it's important to look at dose.

What this does is provide for each individual etoricoxib dose, the summary rates of overall upper-GI events by dose of etoricoxib. You see when you start to break out individual doses you get much more limited amounts of data not only by patient-years of exposure but also number of cases.

What you see here, again, given the

limitations of data, you see a dose trend in terms of GI effects, which again is not surprising, and you see that 30 milligrams here but a very limited amount of data.

Now, of course importantly still is the fact that these doses that we're seeking approval here of 30 and 60 are below the effect size observed with naproxen here.

DR. HERTZ: Do you have a similar slide for the complicated events?

DR. CURTIS: No, we don't because of these limited amounts of data. I think we would probably have literally zero events on 30 milligram in that case.

Now, on the next slide would be thrombotic events. On Slide 225 is a similar display from the development program of thrombotic events by dose. Again, point estimate with a confidence interval around the point estimate for the rate for a hundred patient-years by dose: 30, 60, 90 to 120 milligrams. These are confirmed thrombotic events by dose. Here is the data we have with 30 milligrams relative to

other doses. That complements the blood pressure data that I presented in the core presentation.

CHAIRMAN TURK: Thank you.

Dr. Stine.

DR. STINE: Thank you. Don't go away, don't go away.

(General laughter.)

DR. STINE: Your favorite, Slide 276 (chuckling).

(Staff complies.)

DR. CURTIS: I have that number down.

DR. STINE: I wondered what all those people were doing over there and now I know. They have those laptops going.

From this calculation, you could estimate how many additional thrombotic CV events you get per saved GI event, right, or vice versa?

All right, we were talking about that before. You know, you get three GIs prevented for each CV event that happened or something like that. We talk about these numbers as if these events are comparable. I mean, if you were to put dollar values

on those events and the associated therapy that would come with those events, would that be a reasonable tradeoff?

DR. CURTIS: I mean, I think I have one that said that one has to make these tradeoffs on an individual patient basis. I think that's a value judgment between different types of events. I think different people may not equate a GI event with an MI event.

DR. STINE: You haven't done the health economics analysis? The Europeans didn't make you do that for this? I thought the Europeans required this for the countries that had socialized medicine, that you had to show that you did some sort of reasonable cost/benefit. No?

DR. HOCHBERG: Let me make it clear the European agencies that approved Arcoxia did that on the basis of the clinical data, not including MEDAL because it was done several years ago. They do not require health assessment analyses to gain approval. They require it in individual countries for reimbursement purposes. Of course, none of those

analyses included the MEDAL data, and that was generated on a local level.

DR. STINE: Okay. Then, the second question was, one of the more compelling arguments for this medication seems to be that it helps people that aren't helped by other medications.

We've seen slides that show that the average performance or efficacious nature, this drug is comparable on average with other drugs, but we don't know that it's helping different people than are helped by the other drugs; right? I mean, we could be helping the same people.

The argument here seems to be, "Ah, this will help people that aren't helped by other therapies." Do you have any evidence such as a crossover study or some other experimental evidence that would suggest that, in fact, this drug helps people that aren't helped by the currently approved therapies?

DR. CURTIS: As I said this morning, no, there have been no specific crossover studies. There have been attempts to do that in the literature, and

they are very difficult methodologically.

That doesn't take away from the clinical reality which is something that I'll ask Dr. Hochberg to speak to about the variability of response among agents and the fact that it's very difficult to predict response among individual patients.

DR. HOCHBERG: Thank you, Sean

While there are no specific studies with etoricoxib and comparators, there are a lot of data in the literature which demonstrate the variability in individual response to nonsteroidal antiinflammatory drugs from patients who may be randomized over various periods with a washout included.

There are classic studies, for example, of Huskisson in England or Peter Brooks and Richard Day in Australia showing that about 50 percent of patients will have a clinical response to treatment but some patients will respond to Treatment A but not respond to Treatments B, C, and D.

There are currently no laboratory tests that we can use or clinical predictors that we can use to identify which patient will respond to which agent.

I think Dr. White in her very reasonable comments prior to the lunch break said that one of the limitations in the clinical practice in taking care of patients with osteoarthritis is that patients often run through a series of analgesic agents, including nonsteroidal antiinflammatory drugs, and either fail to have an adequate clinical response to one drug or have toxicity to another drug.

CHAIRMAN TURK: I'm not sure that answered your question actually.

Dr. Jenkins.

DR. JENKINS: I would like to follow up on that question. Dr. Temple is not here today, but he often asks about whether we actually have data showing that nonresponders to one therapy such as an NSAID or a COX-2 when rerandomized back to the therapy they failed or the new agent, you can show that the new agent worked better.

I'm wondering if Merck can comment on whether you have any such data for etoricoxib or Vioxx where you've taken people who have failed on one drug, be it a COX-2 or an NSAID, and then rerandomized them

to either the failed drug or Vioxx or etoricoxib to see if you can see a difference in the effect?

DR. CURTIS: We have not that specific study, no. What we have are robust efficacy data across a variety of subgroups of age; gender; ethnic group; and different joints, knee or hip. The data are very robust in terms of maintenance of treatment effect. Specifically to that specific question and that design, no we've not done that study.

DR. JENKINS: Can I ask you, why not?

DR. CURTIS: Well, Dr. Hochberg I think articulated the limitations in predicting and how you declare and define nonresponders. To methodologically try to evaluate that prospectively is very, very difficult.

DR. JENKINS: That leaves us with nothing more than anecdotes of people saying "I responded to this one, but I didn't respond to that one," so it would be very nice if we could actually have some controlled data that proved that people who don't respond to one respond to another.

DR. CURTIS: Right. Obviously, we all like

and appreciate data, but I don't think the fact that we have not designed that study or run that study due to methodologic limitations really takes away from the clinical reality, which is, these patient satisfaction rates, these switching rates are real. These come from the patients and the physicians.

We can hear from numerous experts that this is the clinical reality in treating the symptoms of arthritis. Therefore, I don't think the absence of a specific study designed to assess that takes away from the clinical reality of a variability in response.

DR. HOCHBERG: I think it's more than just anecdotal observations because it is based on these studies that I referred to earlier which demonstrate variable response for subjects but a similar proportion of response across individual drugs.

CHAIRMAN TURK: Okay. I do need to make a comment. We have about seven people who want to comment. We want to move things along. We have to get to some issues that have to be addressed later. I will call on the ones I have on the list. I will add no more to the list; although, there will be more

chance to discuss these after we finish this section.

However, of the ones who are on this list, you can feel free to withdraw your question, if you feel that we've covered the topic and we don't need to go into detail. Please stay on target, if you will.

Dr. Felson.

DR. FELSON: Well, I sort of have a comment, but I want to ask Merck to respond to it. I think if you put their Slide 276 back up and move from Dr. Stine's earlier question, you can actually make computations not only about the number needed to harm and number needed to benefit, I hate to say this, but number needed to kill or number needed to save, which I think may be of relevance to our consideration.

(Staff complies.)

DR. FELSON: If you use the rate of 5 percent of GI-complicated events, let's assume that the complicated event rate is actually protected against by etoricoxib compared to conventional nonsteroidals rather than some of the data would suggest it might not be, and you use the favorable rate.

I'm going to try to use favorable rates that Merck has presented on Slide 276 comparing to naproxen, which weren't necessarily consistently the rates provided by others.

DR. CURTIS: You want us to stay with that.

DR. FELSON: Yes, stay with that. The relative risk is .4. I think one of the Merck people themselves said it was a number needed to treat to prevent one GI event of 60.

Okay, now 5 percent of those GI events lead to death, if they are complicated events. You multiply 60 times 20, and you get a number needed to save of 1,200 people needed to save one life, okay.

If you take the cardiovascular events, I think about 30 percent of them are fatal events but I'm not sure of that. I would defer a little to cardiovascular people.

A VOICE: (Inaudible comment.)

DR. FELSON: Well, then correct me, okay. The number needed to treat, based on these data, are 1 per 167, okay. It's 167 people that are needed to treat to cause one MI compared to naproxen, to one

cardiovascular event. Now, that's using these data.

If you use the FDA's data or David Graham's data, the number is much less than that, but we're trying to use the more generous estimations here. To be honest with you, I'm not interested in the rate of death of the events that you've enumerated, because most of them are defined as nonfatal events.

I think we are interested in the events that the FDA enumerated because many of those included fatal events. You inflated your numbers, okay, in order to create a number to me that wasn't significant, okay.

I'll use your relative risk, okay, because it's more conservative, but I want to know from the FDA's data what the real events were, not TIAs, not other things that didn't leave anyone with a risk of death. Can someone provide that from the FDA?

DR. CURTIS: Well, we did show overall mortality. Just to be very clear, I mean, I showed you the mortality rates overall. I mean, these are clinical data.

DR. FELSON: You know, please confine

yourself to responding to my question, okay. We're using Slide 276 which you have preferentially placed in evidence here, okay, because it provides favorable data regarding etoricoxib relative to Naprosyn, more favorable than the FDA has presented with respect to cardiovascular risk, which is one of the major considerations.

DR. CURTIS: With all due respect, I showed that because those are the prespecified endpoints for those analyses, overall GI events and confirmed thrombotic events. We were going with the data analysis that we prespecified, so that was the purpose for showing those endpoints.

DR. FELSON: At any rate, regardless, I went through the number needed to kill, okay. Depending on the proportion of people who die, and if it's 20 percent, the number needed to kill is something like you treat 600, you kill one person who would not have been killed were you not to have etoricoxib available to you.

To save one GI death, okay, you treat 1,200 people to save one GI death. The tradeoff is about

two to one. You kill twice as many people as you save, and that's compared to Naprosyn.

That uses conservative estimations presented by the sponsor regarding the relative risk of cardiovascular events in naproxen versus etoricoxib whereas the FDA has presented data that suggests a higher relative risk than that.

CHAIRMAN TURK: That's exactly why I was asking to look at those NNT type data.

Dr. Hertz.

DR. CURTIS: Can I just show one slide, sir?

DR. HERTZ: We're just looking to see which of Rob's slides you're referencing for cardiovascular. I have actually a table from the sponsor's submission that is total deaths, cardiovascular deaths, and thrombotic cardiovascular deaths from the non-MEDAL Program. I will just read you the content of the table.

For naproxen at 1,728 patient-years, we have 5 total deaths, 3 were cardiovascular, so a rate of 1.7. For etoricoxib -- and it's the total, it's not the matched dataset, it's a pooled analysis -- the

patient years were 4,100, there were 10 cardiovascular deaths, for a rate of .24. I can give you the cardiovascular thrombotic deaths, which are slightly different. The cardiovascular deaths were 10 for a rate of .24 for etoricoxib, and 3 for a rate of .17 for naproxen. Cardiovascular thrombotic deaths were 9 with a rate of .22 for etoricoxib and 2 with a rate of .12 for naproxen.

DR. FELSON: That is .22 per 100 per year, is that?

DR. CURTIS: Yes. Dr. Hertz, these are the data, yes.

DR. FELSON: The difference is .1 per 100 per year or 1 per thousand per year?

DR. HERTZ: It looks like.

CHAIRMAN TURK: Dr. Curtis.

DR. CURTIS: I think, Dr. Felson, these are the rates Dr. Hertz was quoting.

(Showing slide.)

DR. FELSON: Okay.

DR. CURTIS: This is the data that supports the mortality slide that I showed broken out by the

individual types of events, and I think Dr. Hertz was focusing on the naproxen events.

DR. FELSON: It's one per thousand per year. That's a difference of one per thousand per year, which is almost exactly what I suggested, which is you would kill one person out of every thousand you treated with etoricoxib of a cardiovascular death compared to naproxen.

CHAIRMAN TURK: Dr. Curtis, did you want to respond?

DR. CURTIS: Well, again, I think that I was just wanting to articulate the overall mortality that we've shown which showed that in the MEDAL Program where we have the largest amount of data, there was no difference. I wanted to also go over the mortality data Dr. Hertz spoke of about.

Thank you.

CHAIRMAN TURK: Dr. Fries.

DR. FRIES: Back to the question of how many NSAID are enough. Despite my practice as a rheumatologist and my esteem for my colleagues in rheumatology, twenty is enough.

The question that we're really trying to answer with this I consider rather weak argument about there is this crying need which comes out because we don't have good treatments for osteoarthritis, good medical treatments, and everybody is dissatisfied with their treatments, so they keep switching around quite a bit.

Perhaps Dr. Hochberg does but I certainly don't give people all twenty to find out if they are going to respond to the twentieth one after they have failed nineteen. The real question is the marginal chance of a response after "X" number of failures, and that number is surely well short of 20.

I think a new drug has to have some reason that you would put it in the top six of your rotation, or it's not going to have very much effect.

CHAIRMAN TURK: Dr. Morris, finally. Sorry.

DR. MORRIS: I had a couple of questions about the proposed risk management plan.

Could you go to Slide 60?

(Staff complies.)

DR. MORRIS: In that slide, you proposed to

lose a class labeling template. I was looking at the second paragraph on the gastrointestinal risk statement. As I read that, I mean, it seems to me that that's pretty much contrary to what you've been presenting today in terms of relative benefit of this drug for gastrointestinal problems.

The question is, does this mean that you're not going to include in your label the data you're presenting or, if you do, wouldn't that be contrary to this label statement, or at least actually make that rather than a warning a benefit because you're reminding people how bad other NSAIDs are?

DR. CURTIS: I'm sorry if I wasn't clear. We're proposing that the NSAID class template level be the basis for the etoricoxib labeling including this risk.

DR. MORRIS: Yeah, but are you saying you're not going to include the gastrointestinal benefits of this drug in your label? Because if you do, that's contrary to that statement.

DR. CURTIS: Well, we think it's appropriate to describe the clinical trials data in a label, but

that this warning would be there.

DR. MORRIS: You're saying you would not modify this statement here but you would include data that says basically compared to other NSAIDs you're better?

DR. HOCHBERG: We would expect to have the robuts clinical trial data described in the label, but we're not sure that the FDA, as was the discussions with Vioxx and celecoxib already, would modify the class language regarding NSAID GI toxicity.

DR. MORRIS: Well, if they don't, isn't what you're going to put in contrary to that statement?

DR. HOCHBERG: No. This is absolutely a factual statement. You can have these serious events when you take etoricoxib. It's just your risk of developing them is lower than, let's say, with naproxen or diclofenac.

DR. MORRIS: Yes, but isn't the effect of all that to say "All of the other NSAIDs are more risky than us"? Isn't that actually going to turn out to be a benefit rather than a warning?

DR. HOCHBERG: Well, we would love

differential language, all right, but what we're not saying is we have no GI effect. Therefore, we think it is appropriate not only in the labeling but in discussions between physicians and patients regarding consent to take the drug and, you know, risks and benefits.

DR. MORRIS: All right.

DR. HOCHBERG: There is a GI risk.

DR. MORRIS: Okay. Let's move on to Slide 62.

(Staff complies.)

DR. MORRIS: The last statement there about "No plans for broadcast DTC advertising at this time," I know we're outside the beltway, but, boy, that sure sounds like an inside-the-beltway statement. What do you mean by that? Does this mean that the day after this drug is approved you can change your mind and change your plans?

DR. HOCHBERG: No, it doesn't.

DR. MORRIS: Are you committing to a time period for which you will not do DTC?

DR. HOCHBERG: We are not committing yet.

We probably would be willing in discussions with the Agency to commit to a time. What we're discussing here and trying to describe is an event-driven trigger. I want to reemphasize we have no plans for television advertising at this time.

What we do commit to, and this is stated in the "Form of Principles For Voluntary DTC Ads," we want to make sure that everybody is aware of the risk/benefits of this drug before we would even consider doing DTC ads at a later date, but we don't have those plans yet.

DR. MORRIS: Well, you're having an educational program to teach physicians about the attributes of the drug, so you will speed up that educational process as part of your post-approval activities. You're going to do these surveys.

I'm assuming that it won't take long. I mean, the only good argument that I've ever heard for no DTC is that it allows you the time, it slows the adoption rate of the drug, and allows you time to accrue risk information.

I don't see in this plan any plans to accrue

risk information. Are you going to have a registry of some sort? Are you going to do something special to accrue this risk information, so we can learn what the risk is in a population? Is that possible?

DR. HOCHBERG: Let me address, first of all, the data from the surveys will not be instantaneous. We estimate it will probably be 12 to 18 months before we would have drug utilization data and physician survey awareness data with which to make an assessment of have we reached steady state, let's say, in terms of awareness, so that's the first point.

Regarding postmarket risk assessment, we do not have plans for a registry at this point. We are willing to discuss options with the FDA, but obviously what kind of risk assessment you need depends on what final label and doses are approved.

Then, you know, we have a robust risk assessment already in terms of the MEDAL Program and in terms of experience in Europe at higher doses. We are willing to talk about multiple options with the FDA, just having had that discussion.

DR. MORRIS: If I understand what you just

said, you would estimate that there would be no DTC for at least the first 12 to 18 months? I mean, my assumption is that you would have to have some kind of a priori level of what you mean by physicians being educated or being aware of these key attributes and they would have to meet that level.

DR. HOCHSBERG: That's correct. We are willing to work with experts in the Agency in terms of designing these surveys that would assess that metric of awareness and figure out where people are comfortable. But, again, at this point we have no plans for a DTC.

DR. MORRIS: The 12- to 18-month estimate is a reasonable estimate?

DR. HOCHBERG: That's a reasonable estimate of how long we think it would take to get the drug utilization data and the physician awareness data, that's right.

CHAIRMAN TURK: Dr. Ginzler.

DR. GINZLER: Yes. To avoid more patient testimonials about the need for other drugs, do you have any specific data from these trials as to the

number of "failed drugs" that patients were on before they entered your trial and how they relate to the efficacy of the 30- and 60-milligram doses?

DR. CURTIS: No. The standard design for the studies was that patients on a prestudy therapy would be withdrawn from that therapy, and if they met a predetermined flare in their osteoarthritis activity, they would then get enrolled. The specific agent and their history of NSAID therapy, we collect that information but that was not a specific part of the study design.

DR. GINZLER: You have essentially selected for responders, since these are people who flared when their successful drug was discontinued, or a more or less successful drug?

DR. CURTIS: Right, but not everybody flared.

DR. GINZLER: If you say they had to flare to come into the study, then you are selecting for responders.

DR. CURTIS: This is standardized. This is how flare-designed OA studies have been run, and we're

following standardized methodology in that regard.

DR. GINZLER: Well, in fact, in rheumatoid arthritis, that's not really how it's done at all. In all of the TNF trials, nonresponders had additive therapy. Drugs weren't withdrawn and wait for a flare.

DR. CURTIS: Right. Well, as we know, NSAIDs manage symptoms. The pain endpoints, those are symptom-based endpoints. We are, you know, assessing patients and picking patients based on symptoms, which is certainly a reasonable, validated methodology in order to evaluate patients.

Now, to your point, on Slide 912 is some information about the breadth of types of prior medications patients have used. This is an example from the MEDAL Program where for each of the three MEDAL study cohorts -- the OA 60, the OA 90, and the RA -- this is a list of prior specific medications.

It at least gives you a sense of the different types of medications patients have tried. Obviously, it gives you just a sense that these are patients who have in the past used a variety of NSAIDs

or COX-2 inhibitors.

DR. GINZLER: That's really all I wanted. I didn't really care whether you gave us specific data on each agent, just how many agents were used.

DR. CURTIS: Okay.

CHAIRMAN TURK: Dr. Jenkins.

DR. JENKINS: Following that same line of questions, I would like to come back to the question I asked earlier about evaluating the efficacy of the COX-2 agents in people who had failed another therapy. As part of the package that was handed out during the open public hearing, there is reference to "Study 906," which was a comparison of rofecoxib versus celecoxib in patients who show inadequate clinical response to celecoxib.

You apparently have conducted a study where failures to celecoxib were randomized back to celecoxib and rofecoxib. I'm wondering, do you have a slide with the efficacy results from that study?

DR. CURTIS: I answered your question in regards to etoricoxib. I was not aware of that study. I might ask one of my colleagues who might be aware of

that study to comment.

DR. JENKINS: I would just say I asked specifically about etoricoxib or rofecoxib when I asked.

DR. CURTIS: Okay. All right. I'm sorry I didn't hear your question correctly, then.

DR. HUANG: Dr. Jenkins, Protocol 906 was actually not a study of patients who showed that they failed treatment but was only a study conducted on patients who self-declared as having failed on celecoxib, so it wasn't clear how to interpret those results.

DR. JENKINS: Do you have the results is the question I'm asking. Because it says "In patients who show inadequate clinical response to celecoxib." It was a four-week study of 25 milligrams of rofecoxib versus 200 milligrams of celecoxib, total daily dose.

I'm just wondering what did you find in that study, given the questions and limitations about whether people were truly nonresponders? I'm just curious, we keep hearing about people respond to one and they don't respond to another.

Here is a study that Dr. Temple has been calling for, for a long time, and I would be interested in knowing what you found.

DR. HUANG: That study didn't demonstrate a difference between treatment arms. But, again, I want to clarify that study doesn't actually fit the description that you're talking about because it did not have a run-in period where we saw and were able to verify that the patients were nonresponders.

DR. JENKINS: You did the study. Why did you design it that way if you felt that it wasn't going to be adequate to answer the question?

DR. HUANG: I can only tell you what I've already said, which was, the limitations of the study as it was designed was it did not demonstrate patients were failure to the prior treatment before they initiated in the study.

DR. JENKIN: I just point this out because I think it would be information for the Committee to consider as you're discussing the issue of approvability. You know, what benefits does this drug bring to the list of twenty that I think we heard

about earlier versus what risk does it also bring as you're weighing those factors? This is not an etoricoxib study; this was a rofecoxib study.

It is interesting that we keep hearing about anecdotes. Even Dr. Temple might tell you that anecdotally he has had the same observation personally. But that's not the same as having data to actually show that people who don't respond to one, respond to another one. That would be very powerful data to have to offset questions about increased risk.

DR. VAN ADELBURG: Would you allow me? My name is Janet van Adelburg. I'm senior director at Merck Research Labs and I'm a little more familiar with the famous Protocol 906. Since I was running in the hall, I may repeat some of the things that my colleagues have said.

This was a study that attempted to look at this very important question. It was patients who were treated with celecoxib who then were switched to celecoxib or rofecoxib.

The point of the study was, in fact, as you've heard there was no difference between the

groups. The limitations of the study were that there was no definition of nonresponse.

I think it's the first attempt in an area that is quite difficult to look at, which is, how do you get at who responds and who does not and understand in a clinical sense what predicts response to different NSAIDs or to other therapies?

There have been very few studies on this in the literature. The Hunziker study is really one of the few. I think what we can say from Protocol 906 is that this was not a study designed that was effective in showing a difference, but I think what we can also say from it is that doesn't mean that differences don't exist. We just don't quite understand how to measure them yet. Does that speak to some of your question?

DR. JENKINS: Again, I'm raising it just for the Committee's attention to understand that sometimes when we see a drug that has an increased risk over available therapy, the risk can be acceptable if you also have an increased benefit.

This is just looking at the relief of pain.

You will have to also factor in whether you think there's any benefit on the GI side and you've been having a lot of discussion about whether the benefits of the GI effects in some way offset or mitigate the cardiovascular effects, particularly against naproxen.

This was just looking at, on the efficacy side, does this work better than the drugs we already have. I thought it was an important study to hear a little bit more about, even though it is not an etoricoxib study.

DR. HUANG: While it's not an etoricoxib study, we will get the data and we will be able to present it after the break.

CHAIRMAN TURK: What break?

(General laughter.)

CHAIRMAN TURK: Thank you.

Dr. Day, you've been waiting very patiently. This will be the last question, and then I'll try to summarize.

DR. DAY: Thank you very much.

To go back to the risk management program, I was pleased to see where was something like six

components in it.

DR. DAY: To go back to the risk management program, I was pleased to see there were something like six components in it and pleased to see no DTC at this time planned as Dr. Morris has pointed out. However, as Dr. Crawford has also pointed out, all of them are likely covered with no real sense of how they would be conducted.

I am particularly interested in the role of physician in prescribing the drug because of past experiences with other products in this class. There is a physician survey about awareness is one of the components and another is to test educational materials with both patients and healthcare providers.

My question is, would you consider the methodology of label comprehension studies to be done with physicians as well as patients early on; and if so, what key educational messages or key contact messages would you want to test for? It gets down to, what are the key messages that a physician must know and understand in order to safety prescribe and monitor patients?

DR. HUANG: Dr. Day, certainly the physician circulars are not typically tested for physician comprehension. I'm not sure if the FDA-mandated "Med Guide" was tested either. What we normally test in the past are the drug-specific, patient-package inserts. We do comprehension testing on that for the patients.

We don't normally do comprehension testing of physician materials. We assume a certain level of, you know, awareness. What we are proposing to do in terms of testing key awareness is to make sure that physicians understand that (a) this drug and others in the class do have an associated CV risk;

(b) This drug and others in the class do have an associated GI risk, this is not placebo in terms of the GI tract; and

(c) This drug and others in the NSAID class can raise blood pressure, and are they aware of the language in the circular that was shown before that says blood pressure should be monitored when these drugs are used, all right, you know, in addition to other routine precautions.

Those are the kind of key safety-related messages that we want to make sure they are aware of.

DR. DAY: In your briefing document in several places, it says to watch out for dose and duration. For dosage, people start at 30 milligrams. What kicks them up to 60? Furthermore, what do you do about duration. OA isn't going to go away, so what happens to the long-term?

DR. HUANG: That was part of the drug utilization studies that we're looking at where in these claims databases and other mechanisms we would look at what percent of patients are started on thirty, and then try and understand when the physician made the decision to titrate up to sixty, what made that decision, okay, what clinical characteristics.

DR. DAY: You would have no advice as to when to do that? There would be nothing in the label? There would be some observation or endpoint?

DR. HUANG: Our experts tell us normally you may need four weeks to see perhaps the maximal effect, two to four weeks. We would suggest waiting at least that amount of time before a physician makes a

determination to try a higher dose. Of course, they also would have assessed tolerability at the 30-milligram dose before they have made a decision to try a higher dose.

DR. DAY: What about duration?

DR. HUANG: Duration is interesting because a minority of patients take these medications every day for osteoarthritis. What's more common, when you look at actually usage data from IMS or other places, the median number of days treated in a year for chronic users of NSAIDs is about 60. The mean is about 110 or 112.

Most patients are not taking an NSAID every single day even if they report that they are taking it chronically. That may be different than what the rheumatologists on the Committee see. Because obviously they are seeing a little different spectrum, not the average patients for OA, and that's certainly not true for RA, but for osteoarthritis in the community the average duration is about 112 days in a year.

CHAIRMAN TURK: Thank you.