and also observed in patients who took aspirin at low doses on a regular basis. We have also established a favorable hepatic safety profile for etoricoxib.

Regarding the renovascular effects, in particular the blood pressure, we have shown a dose-related effect for etoricoxib, again, which is consistent with the NSAID class and the mechanism of action of these compounds with effects observed between those seen with the traditional NSAID comparators, specifically naproxen and ibuprofen.

It is important, again, to reiterate that blood pressure is an important adverse event of all NSAID including etoricoxib, but it is a monitorable adverse event and it can be managed.

We spent extensive time discussing the thrombotic cardiovascular safety profile of etoricoxib, and it is very consistent with prior randomized clinical trials data of other COX-2 selective inhibitors versus traditional NSAID.

As reviewed by Dr. Cannon, there is an unmet need in the management of osteoarthritis. Patients need additional options, and we believe etoricoxib

represents an additional valuable option. It has a well-established and favorable risk-to-benefit profile in patients with osteoarthritis who require an NSAID therapy.

It provides pain relief, an improvement in physical functioning, and an improved GI and safety and tolerability in comparison to traditional NSAID based on an extensive development program and includes the findings from the MEDAL study, which really do show for the first time based on outcomes that inpatients on a PPI, there is an added benefit to a COX-2 versus a traditional NSAID, an important finding for the treatment of high-GI-risk patients in the thrombotic cardiovascular safety profile, again, consistent with the profile of other NSAID with the exception of naproxen.

Thank you very much for your time and attention.

CHAIRMAN TURK: Thank you, Dr. Curtis and the other presenters from the sponsor. Are there any clarifying questions for Dr. Curtis or for the two preceding speakers?

MS. CRAWFORD: Thank you. I have a question, Mr. Chair, for Dr. Curtis. Could you please comment on whether or not the clinical study designs enabled valid comparisons as to whether there were observed differences in adverse effects among racial groups, especially with the renovascular safety but in general as well?

DR. CURTIS: We have looked at subgroups by ethnic group, and there appears to be a consistent profile across all ethnic groups. No specific differences observed.

CHAIRMAN TURK: Dr. Cannon?

DR. R. CANNON: Was there any difference in the MEDAL Program between etoricoxib and diclofenac in onset of atrial fibrillation? I didn't see that mentioned in your presentation or the background materials. I would be concerned that a drug that might increase blood pressure and retain fluid could provoke atrial fibrillation.

A followup to that question is, of the patients who had either or a nonfatal cerebrovascular event, ischemic or cerebrovascular event, was there

any difference in atrial fibrillation as possibly being the underlying precipitating event for those patients?

DR. CURTIS: There was a higher incidence in the 90-milligram comparison for etoricoxib to diclofenac and atrial fibrillation but not in the 60-milligram group. In regards to your question about the patients with strokes, if you could, clarify that question please, Dr. Cannon.

DR. R. CANNON: Did the strokes, fatal or nonfatal, occur in the absence of atrial fibrillation or did they accompany onset of atrial fibrillation? Is it known what the relationship of the cerebral vascular accidents was in relationship to atrial fibrillation.

DR. CURTIS: The majority of those events occurred in patients without atrial fibrillation.

CHAIRMAN TURK: Dr. Day, your question?

DR. DAY: Concerning the unmet need, one of the ways to assess that is to look at patient switching. Since this product has already been marketed in many other countries, are there any data

about switching from this product, the percentage of patients or the duration on the agent before switching?

DR. CURTIS: We have no specific studies that have looked at switching with this product.

DR. SANDBORG: Were cardiovascular events, especially stroke, increased in those patients who had an increase in blood pressure?

DR. CURTIS: Since there was no difference in -- I'm sorry. Could you clarify the question, please?

DR. SANDBORG: Was there a higher proportion in those patients who had elevated blood pressure on the medication where those patients have an increase, a further increase, over the baseline increase in cardiovascular events?

DR. CURTIS: As you saw, the primary result was that there was no difference in strokes and heart attacks, the composite.

DR. SANDBORG: Right.

DR. CURTIS: We certainly looked at patients with a baseline history of hypertension and looked at,

as I showed in the core presentation, all established risk factors for heart disease and showed no treatment by subgroup interaction across those high-risk subgroups. We did not specifically look at postrandomization elevations in blood pressure as a subgroup.

CHAIRMAN TURK: Let me caution you that when you have raised your hand or been acknowledged, that we are keeping a list and I will call on you in the order that we have the list.

DR. DAVIS: Referring back to Slide 41 in the MEDAL Program, looking at the incidence of GI events, there is no difference in complicated events between the two drugs, and then on Slide 43 you break it down just for overall upper-GI events broken down by aspirin users and PPI users. Have you done that for the complicated events?

DR. CURTIS: Yes, we have and there was no difference among these subgroups in the complicated events, consistent with the overall lack of significant difference between the two treatment groups for complicated events.

DR. DAVIS: Okay.

DR. CURTIS: This result in overall events, this was driven by the symptomatic or uncomplicated ulcers.

DR. DAVIS: A second question for the MEDAL Program, you showed a nice summary slide looking at the 60-milligram dose composite with CHF discontinuation, hypertension, edema. Do you have one similarly for the 30-milligram cohort? Because that is the dose that is going for indication.

DR. CURTIS: Right. Of course, in the data for 30 milligrams come from the non-Medal portion of the program, from the Development Program, and since 30 milligrams was not included in the MEDAL Program I can't show you those data.

The data for congestive heart failure with 30 are limited to the Development Program, both the placebo comparison, which I showed 6-month data versus celecoxib in which there was no difference in heart failure between etoricoxib 30 and celecoxib, and the one-year-long data versus naproxen, but not for MEDAL since that wasn't included as a dose.

CHAIRMAN TURK: Dr. Felson.

DR. FELSON: Many of our osteoarthritis patients are older with lots of comorbidities. The MEDAL Program's inclusion and exclusion criteria I don't believe were stated. Can you review that please and tell us if any of these patients had comorbidities or high risk of any of these events?

DR. CURTIS: The MEDAL Program, the minimal age for inclusion was 50 years old, so the mean age was 62. We had patients as old as in their nineties in MEDAL.

We have looked at both general cardiovascular and GI safety by age in the MEDAL Program. We show the absolute risk of a CV and GI event go up with age, but the between treatment relationship -- that is, no difference between etoricoxib and diclofenac -- is maintained in the elderly.

DR. DAVIS: Let me just follow that up by asking, were there any exclusions of people who had MIs or CHF or known cardiovascular morbidities?

DR. CURTIS: Yes. The patients could not be

enrolled within six months of an acute coronary or cerebrovascular event, so anyone six months after a heart attack or stroke or coronary surgery could be included but not within six months of an acute event. Does that answer your question?

DR. DAVIS: A little.

DR. CURTIS: Again, that was primarily to ensure that medical stabilization of their acute condition had been managed appropriately. The issue of anticoagulant use, we want to make sure that all those sort of appropriate acute postcare issues have been stabilized, the medical management was stable, before someone would enroll in a clinical trial.

DR. DAVIS: I guess, in followup, it would be nice to know if the rates seen in the trial were similar to the expected rates in an age and gender match population that was not in the trial.

While eligible for this trial, I guess I wonder about whether physicians allowed their patients in a trial that might put them at risk of an event. It would be nice to know actually how many people in this trial compared to, say, a normal population of

this age had a history of events like that or whether there was sort of a selection of exceptionally healthy people who might not necessarily be similar to the ones who are going to get this drug.

CHAIRMAN TURK: Dr. Ginzler.

DR. GINZLER: Yes. I wonder whether in your analysis you look at the confounding variable of an exercise regimen in patients in the trial. You know, how many of these people were couch potatoes? How many of them worked out in the gym?

DR. CURTIS: Well, we certainly have looked at a variety of subgroups, but that specific factor no. I can tell you, I mean, that is to some degree the beauty of a large trial like this where you have 17,000 patients in a blinded fashion randomized to one or two treatment groups, and we can show based on all the characteristics we did look at things were very well balanced between the two treatment groups. I would expect that it would have been balanced.

DR. GINZLER: What did the protocol allow in terms of treatment with antihypertensives or diuretics following that identification?

DR. CURTIS: We of course had broad investigator latitude to treat all concurrent medical conditions, specifically regarding hypertension. We broadly and consistently communicated JNC 7 guidelines to the investigators and had them follow those guidelines appropriately.

DR. GINZLER: Were there differences in treatment?

DR. CURTIS: With antihypertensive treatment?

DR. GINZLER: Or, diuretic treatment.

DR. CURTIS: Yes, there was. There was a difference favoring diclofenac, again, consistent with the difference in adverse event rates. As I showed in the core presentation, the rates of hypertension discontinuations were higher for etoricoxib compared to diclofenac, 60 milligrams.

When you looked at the use or new use or increased use of antihypertensive medications, a similar finding was seen, higher on etoricoxib than diclofenac.

CHAIRMAN TURK: Dr. Saag.

DR. SAAG: In the MEDAL Program, you didn't show data looking at the reasons and levels of discontinuation and dropout. I'm interested in knowing that and also knowing about how you captured adverse events in people that did not complete the study.

DR. CURTIS: Okay. Well, I can show you the summary of the disposition of patients, if you would like. The reasons were balanced with the exception of discontinuations for lab adverse events, which were higher on diclofenac as compared to etoricoxib.

Otherwise, the overall discontinuation rates for adverse events -- Slide 920, please -- summarizes the patient disposition in MEDAL. As I mentioned, there were the 334,701 patients randomized, and everyone who was randomized received at least one dose of study therapy. Therefore, you see the total number of patients who started treatment in the two arms.

Again, this is etoricoxib both 90 and 60 together. This is everything, OA and RA, together. You see rates of overall discontinuations were similar when you break this out by reason, pretty similar with

the exception of a higher rate of lab adverse events, which frankly on diclofenac was largely due to elevations in liver function tests.

When you look at lack of efficacy, protocol violations and withdrawal of consent, which frankly was much higher in this protocol than we typically see, you have to remember this study was enrolling during the whole referral on coxibs both in Europe, again this was a worldwide protocol, 40 countries, as well as the voluntary withdrawal of Vioxx in 2004.

Patients for a variety of reasons did discontinue from a trial which included a COX-2 inhibitor but, that being said, it was similar between the two treatment groups, and all the other reasons are generally similar.

Your second question, Dr. Saag?

DR. SAAG: Having to do with what special efforts were made to capture the cardiovascular outcomes in those patients who discontinued, the 50 percent of patients who in each group were not carried through to the end of the study?

DR. CURTIS: Well, we have an extensive

effort. We had scheduled follow up by phone every six months for patients who discontinued early. We went to extensive efforts with patient-locator services on a worldwide basis. As you saw from that slide, we were able to get the true loss-to-followup rate for patients down to less than 1 percent.

We did absolute due diligence in trying to identify every single patient who discontinued early, but in a large trial of 34,000 patients one cannot find every single patients.

CHAIRMAN TURK: Just as a reminder, we are asking clarifying questions now and we will have another opportunity later, after the lunch break, to go into more detail and some specifics.

Ms. Aronson.

MS. ARONSON: Dr. Saag asked the majority of my question. The 53 percent dropout rate, is that standard?

DR. CURTIS: Yes, it is. In fact, it is in many ways better than is observed with other trials. We anticipated approximately a 20 percent discontinuation rate after the first three months and

a 40 percent discontinuation rate after a year.

We have obviously done a lot of NSAID-type trials, and what we saw with MEDAL was very consistent with that. Actually, the fact that this was a much longer trial actually overall we were quite happy, frankly, with this discontinuation rate. It is typical. It does seem high, but it's very standard.

CHAIRMAN TURK: Dr. Pasricha.

DR. PASRICHA: Yes. I have three questions related to the GI profile of these drugs. I will ask them one by one. The first is, did you see a reduction in the absolute risk of complicated GI events in those patients who were receiving PPI prior to randomization in either group?

DR. CURTIS: I'm sorry, could you ask your question again. I want to make sure I understand.

DR. PASRICHA: Was there a reduction in complicated GI events in those patients who were on a PPI prior to randomization compared to those who weren't?

DR. CURTIS: We saw a reduction in the ulcers, the symptomatic ulcers, but not the

complicated events.

DR. PASRICHA: The use of a prior PPI did not affect the risk of complicated GI events with either drug?

DR. CURTIS: That's correct.

DR. PASRICHA: Okay. Did you do an analysis of the GI adverse events by risk factors for peptic ulcer as previous history or age?

DR. CURTIS: We have looked at risk factors. We have looked at subgroups based on prior history of upper-GI event by age, by gender, and by steroid use and antiplatelet use. I can show you some of those data, if you would like.

We showed that the absolute rates of events were higher in patients with those risk factors, but the relative treatment benefit was maintained. Let me show you on Slide 1074 a risk factor using the baseline risk factors that I just mentioned, again: age, baseline steroid use, antiplatelet therapy use, and prior history of upper-GI perforations and ulcers you see that based on the number of risk factors the rates go up in both treatment groups.

For example, patients with no risk factors had these rates with this relative risk of etoricoxib to diclofenac. As you add risk factors, the rates went up and the relative risk was maintained.

DR. PASRICHA: If I understand this correctly, with more than four risk factors the benefit is less?

DR. CURTIS: That's correct based on this.

If you could, show that slide again, please.

(Staff complies.)

DR. CURTIS: The number of events in patients with four risk factors is quite small. There are only two patients with events on etoricoxib and three patients on diclofenac. Your statement is true but you can look at this confidence interval, which is quite wide.

DR. PASRICHA: Thank you. The final question is about dyspepsia in the two groups. Did you look at that specifically?

DR. CURTIS: We did and we showed about a 25 percent risk reduction in dyspepsia with etoricoxib versus diclofenac.

DR. PASRICHA: Was that significant?

DR. CURTIS: Yes, it was.

DR. PASRICHA: Thank you.

CHAIRMAN TURK: Dr. Levine (pronouncing "le-vine").

DR. LEVINE: Dr. Levine (pronouncing "le-veen").

CHAIRMAN TURK: Sorry.

DR. LEVINE: That's all right.

This is a very real-world study in that you had aspirin and PPI. I wondered in the same group what percent of patients in this population had corticosteroids. Because aspirin certainly completely blocks or practically completely blocks the beneficial effects of COX-2 or traditional NSAID and PPIs are protective.

Can you tell us, have there been any subcohort population analysis of the patients? What percent of patients did have corticosteroids? Corticosteroids in that type of population are considered possibly a deleterious event, a prognostic event, in GI complications.

DR. CURTIS: Slide 1070 is a subgroup of the pooled MEDAL upper-GI clinical event data, so these are the overall events. This is a subgroup analysis by baseline use of corticosteroids.

As you see, the percentage of steroid use based on total patient years at risk is about 15 to 20 percent. Okay, I think it's 16 percent exactly. About 16 percent of the patients were on baseline use of steroids. Obviously, that was largely, if not exclusively, the RA patients.

What you see of course, as expected, the absolute rates of upper-GI events in MEDAL went up with the use of corticosteroids but that this treatment by subgroup interaction for this subgroup analysis was nonsignificant, indicating that the treatment benefit was maintained in overall events in patients on baseline steroid use.

DR. LEVINE: Yes, but did you go further and do a subcohort analysis with patients on glucocorticoids plus aspirin, minus aspirin, plus PPI, minus PPI? This is such a heterogenous group, and it may be a statistical problem, but I think it's doable.

DR. CURTIS: We have not done that specific analysis.

DR. LEVINE: Thank you.

CHAIRMAN TURK: Dr. Cannon.

DR. R. CANNON: Nothing.

CHAIRMAN TURK: Dr. Fries?

DR. FRIES: On Slide 41, I would like some clarification on the criteria, the prespecified criteria, for ulcer determination. My interpretation looking at this slide is that there is a reduction of the incidence of endoscopic ulcers but not one of complicated ulcers at all for this agent. If that interpretation is correct, it seems a little out of sort with meeting the unmet need type of hypothesis.

DR. CURTIS: As I said, there were no routine endoscopic surveillance scheduled through this program. Anyone who had ended up having an ulcer as confirmed by criteria was someone who, frankly, like clinical practice, presented with signs or symptoms suggesting an upper-GI issue, and based on investigator assessment went on to have a diagnostic evaluation.

Just to be clear, this is not a result of routine endoscopic evaluation, but the actual diagnostic criteria for ulcers were established. I don't know if Dr. Lane would like to comment on exactly what those criteria are, but they were validated, prespecified criteria that showed objective evidence of bleeding, or in this case ulceration.

DR. LANG: Just briefly, again, the patient had to be sent for usually symptoms, presumably it could have been a decrease in hemoglobin as well, and would have gone normally for an upper endoscopy, theoretically they could have had an upper-GI series, but it would normally be an upper endoscopy.

Again, it is supposed to be simulating real-world practice where a rheumatologist or a primary care physician thinks an endoscopy is necessary.

CHAIRMAN TURK: Thank you very much.

We are now going to move on to the presentations from the Food and Drug Administration. We will start out with a presentation by Dr. Robert Shibuya, who is a medical officer in FDA. He is going

to be speaking about the medical review of the etoricoxib application.

Dr. Shibuya.

I might say, while they are getting set up, that there will be an opportunity to ask additional questions of the sponsor after lunch.

FDA PRESENTATION

MEDICAL REVIEW OF ETORICOXIB APPLICATION

(PowerPoint presentation in progress.)

DR. SHIBUYA: Good morning. Over the past hour and a half or so, we have heard from the Applicant regarding the rationale for and a review of the safety and efficacy for this product. In my presentation, I will review specific elements of the application that we think are important for your consideration. I will start with efficacy, and I will make it brief.

There is little doubt that etoricoxib is efficacious for OA at doses of 30 and 60 milligrams per day. It's been shown in six separate Phase III trials. However, we do note that the 30- and 60-milligram doses have not been tested head to head

in Phase III.

Therefore, to justify the approval of the 60-milligram dose, the Applicant referenced Study 007, which was submitted and reviewed in a previous review cycle.

Briefly, Study 007 was a Phase II dose-ranging study. We saw the results actually represented slightly differently in the Applicant's presentation. It compared placebo and five doses of etoricoxib. These are the results for Part I of the study.

In this figure, the three co-primary endpoints -- WOMAC pain, a patient global, and investigator global -- are represented in three separate panels. Again, a more negative value is indicative of efficacy.

As we can see there, with regard to the point estimates there appears to be evidence of dose response to 60 milligrams, but that is lost at 90 milligrams. We do note the wide confidence intervals, though.

As you noticed in my description of the

previous slide, these were the results from Part I of this study. Study 007 continued for an additional eight weeks at the 14 weeks.

In Part II of this study, patients were reallocated to either 30, 60, or 90 milligrams of etoricoxib or 150 milligrams of diclofenac. This plot represents the efficacy data, again a more negative value, as evidence of analgesia for the WOMAC pain subscale over the entire period of the study. The important thing to note is that the apparent dose response between 30 and 60 milligrams observed at 6 weeks diminishes with time on drug.

We note the limitations of cross-study comparisons. However, the six pertinent Phase III OA studies were very similar in design. When we examined the treatment effect across studies, and again negative values are evidence of efficacy, we note that the treatment effect size is, roughly, the same regardless of the dose of etoricoxib.

Each Phase III study contained an active control, either ibuprofen, naproxen or celecoxib. However, we note that no trial suggested that

etoricoxib was superior for efficacy over that active control.

Shown here at the pain curves for Study 077, it is the WOMAC pain subscale, that shows that the analgesia was virtually identical to celecoxib. As the Applicant has outlined, the safety data for etoricoxib are divided into two parts, the MEDAL Program and what I will call the non-MEDAL. I think I missed one? No, sorry.

Obviously, for a new NSAID the safety program is going to be quite considerable. In the next slide, I'm going to briefly describe what the Applicant has generated and submitted.

The program consists of the MEDAL Program and what we call the non-MEDAL database. I'm going to summarize the differences here. The MEDAL Program is characterized by its homogeneity. It has a single comparator, diclofenac, and only two doses of etoricoxib, 60 and 90 milligrams. The patient population was limited to OA and RA.

As the Applicant has stated, the sample size is large, almost 35,000 patients with substantial

followup with means of 20, 19, and 9 months for the component studies.

The non-MEDAL database by comparison is very heterogeneous. It is comprised of the 18 conventional Phase II and III studies. It contains two additional study populations, ankylosing spondylitis and chronic low-back pain. The duration of time on therapy is also quite a bit shorter than MEDAL, only up to 52 weeks.

It does have the advantages of additional controls: placebo, ibuprofen, naproxen, and celecoxib. It also has a broader range of etoricoxib doses tested, between 5 and 120 milligrams. We do note that the non-MEDAL database in terms of size is dwarfed by the MEDAL database with their being only about 4,500 patients treated with etoricoxib.

Certainly, a new NSAID or coxib requires a thorough and comprehensive cardiovascular evaluation as part of the new drug application. In the next section of my talk, I will address the cardiovascular findings in the etoricoxib application.

There is really very little need to go over

this. This is a summary slide of the APTC events for the pooled MEDAL Program that show that the relative risks are close to one with confidence intervals that go through one.

We were interested, though, in whether or not there was dose response with regard to the cardiovascular events, so in this slide we've done a subset analysis of the OA patients only subsetted by dose. As you can see, there does seem to be some evidence of dose response where the relative risk increases from 1.07 to 1.30 with the increase in dose.

In addition to looking at the relative risk, which is a very common statistic for making such comparisons, we have also looked at the attributable risk.

In this slide, you can see the difference in how the two statistics are calculated. Relative risk is the quotient of the event rate in Group A and in Group B as estimated by the COX proportional hazards model. Attributable risk is the arithmetic difference in event rates between Groups A and B.

The value of the attributable risk analysis

is that it can help us understand the number of excess patients who might experience an APCT event if taking etoricoxib instead of diclofenac. We can use that concept when we are assessing the risk-to-benefit ratio.

In this slide, we see the same subgroup analysis, this part of it that was previously shown. Again, the patients are limited to OA and are grouped by dose. This particular slide also shows the aggregate statistics and has this additional column that is called the "difference in risk," which could also be perceived as the attributable risk.

When we look at the relative risk for the 60-milligram dose shown here, it is nearly one. However, what does that mean when we assess the potential for excess events?

I draw your attention to this cell, which is the attributable risk with its associated confidence intervals because those values are used to make the estimates that we will see in the next slide.

Based upon the attributable risk analysis done by our statistical team, I have summarized the

possible effect of etoricoxib administration to large populations under three scenarios: a most likely, a high estimate, and a low estimate.

Under the assumptions that a thousand patients could be exposed in a year, the analysis shows that 490 excess patients would be expected to experience an APTC event on etoricoxib than if they had taken diclofenac.

As a high estimate, defined as the upper limit of the 95 percent confidence interval, that number of excess cases increases to 2,300 cases. A low estimate, which we would define as the lower limit of the 95 percent CI, predicts that 1,300 fewer events could occur.

We also reviewed the non-MEDAL database to inform for the risk for cardiovascular events. There is little to say about this. The Applicant has already gone over it. I will only point out the bottom two lines, which show the rates and relative risk for the comparisons versus naproxen.

These are really the most robust data here in terms of numbers of events and drug exposure. We

note that the relative risk versus naproxen is 2.72, with a confidence interval that excludes 1.

This concludes our review of the cardiovascular safety section. To summarize the cardiovascular safety data, as assessed by relative risk, the pooled MEDAL data show comparable cardiovascular risk versus diclofenac.

However, given the 95 percent confidence interval, the attributable risk for etoricoxib compared to diclofenac could be as high as 2,300 excess events per 1 million patient-years.

The non-MEDAL database suggests that etoricoxib is inferior to naproxen. The predominant rationale for the development of the COX-2 inhibitors was the theoretical advantage with regard to gastrointestinal safety.

As we have heard from the Applicant, GI events were an important endpoint in the MEDAL Program. In this part of my talk, I will summarize these GI safety findings.

There is little to discuss here. What I was going to do was talk about the difference between

complicated and not complicated, but that has already gone on in the previous Q-and-A session.

This really does not require an explanation, either. The difference that was observed which attributes benefit to etoricoxib was really only for the combined cases including the not-complicated ulcerations.

I will spend a couple of minutes or, hopefully, a minute talking about this slide. Again, what I've done is I've broken down the possible event categories into ulcerations, perforations, obstructions, and hemorrhages.

We have looked at complicated and combined including the not-complicated events. What you can see is that the excess events really fall within the ulceration category.

With regard to the lower-GI safety for both the complicated and combined cases, there was some slight numerical superiority for etoricoxib over diclofenac.

When we look to the non-MEDAL database, we see that the event rate was substantially lower for

etoricoxib, .44 to .97 and .93 to 2.32, regardless of whether or not the analysis included the complicated events only here or both complicated and not-complicated events.

These significant differences between conventional NSAID in etoricoxib in the non-MEDAL Program were largely driven by the comparisons to naproxen. Here we see a Kaplan-Meyer estimate that shows the difference between etoricoxib and naproxen in the non-MEDAL database.

In addition, you have heard the Applicant discuss other measures of GI tolerability such as discontinuations for dyspepsia and abdominal pain and for laboratory abnormalities such as an otherwise unexplained decrease in hemoglobin.

These analyses are summarized here. As with the ulcerations without significant medical consequence, etoricoxib was found to be superior for these kinds of signs and symptoms.

To summarize the effects of etoricoxib on the GI tract, we conclude that for medically significant upper-GI events, etoricoxib approximates

diclofenac and appears superior to naproxen. Second, for non-serious GI-related symptoms, etoricoxib is superior to diclofenac and naproxen.

A side-effect of the NSAID class is hypertension, retention of salt and water, and elevations in BUN and creatinine. These event effects have been collectively termed "renovascular." The next section of the presentation deals with the renovascular safety findings.

To put the findings for renovascular safety into context, I will briefly review two large epidemiologic studies assessing the effects of blood pressure on large populations. The Multiple-Risk Factor Intervention Trial, or "MR. FIT," published by Neaton, et al., in 1992 is the first such pertinent study.

Mr. Fit was a randomized, multicenter, primary-prevention trial to study the effect on the incidence of coronary artery mortality of interventions to blood pressure, cholesterol, and cigarette smoking. The study followed over 316,000 men for a mean duration of 12 years. This figure

summarizes the blood pressure findings from "MR. FIT." On this axis is the systolic blood pressure between 120 and 160 millimeters of mercury and on this axis the diastolic between 70 and 100. The columns show the death rate due to coronary heart disease.

What is evident is that for each group of diastolic blood pressure measurements, say, along this row (indicating), there is a steep rise in death due to ischemic heart disease with increases in systolic blood pressure. The effect is not as pronounced for the diastolic blood pressure.

This slide shows summary data from the prospective studies collaboration. These authors conducted a meta-analysis of 1 million adults in 61 prospective observational studies to evaluate the effects of blood pressure on mortality.

On the left panel, the mortality due to stroke is plotted versus the systolic blood pressure between 120 and 180 millimeters. We see a steep increase in the stroke incidence with increases in systolic blood pressure for each decade of life at the time of death.

In the right panel, we see the identical depiction, this time for deaths due to ischemic heart disease, but again showing the steep increases with increases in systolic blood pressure.

After this review of the effects of elevated blood pressure on large populations, let's move on to the specifics of the etoricoxib safety program. In the MEDAL Program the Applicant evaluated the negative effects of etoricoxib and diclofenac on the renovascular system in four areas: effects on blood pressure, rates of congestive heart failure, rates of edema, and rates of patients who develop pertinent laboratory abnormalities.

With regard to the evaluation of the effects of these drugs on blood pressure, they looked at four things: discontinuance, discontinuations for hypertension-related AEs; hypertension-related AEs, which would include the severe events requiring discontinuations and less severe events; they also collected vital signs data, which were plotted and the mean difference in baseline for the blood pressures were analyzed; and they also prespecified certain

increases in systolic and diastolic blood pressure and calculated the proportions of patients who meet such thresholds.

Let's move to the actual results for MEDAL. This table, which is from the Applicant's submission, summarized pooled MEDAL data for hypertension. I'm going to spend a moment describing how the data are organized because the next several tables use an identical format.

Each component study in MEDAL is given its own row, except that the MEDAL study itself has two rows to reflect the two study populations. The rheumatoid arthritis patients are placed on the right side of the page, the remainder of the page is the OA patients, and this (indicating) line separates the patients who receive 60 milligrams versus the remainder of the patients who receive 90 milligrams. For each study and dose and patient population we can make pairwise comparisons.

This particular table shows the discontinuations due to hypertension-related AEs. In making the pairwise comparisons, say, in this set of

three cells or is set of three cells, we see that for every study, for every dose, and for every patient population etoricoxib had a consistently higher discontinuation rate. There also seems to be some dose response in this finding when you look at the difference in proportions between 60 and 90 milligrams.

For brevity, this is the only table that I've included that contains data related to the relative effects of etoricoxib and diclofenac on blood pressure, but the other analysis all lead to the conclusion that etoricoxib has more deleterious effects on blood pressure than does diclofenac. Importantly, MEDAL provides no information regarding the effects at 30 milligrams.

This is the analogous table for the findings of discontinuations due to edema. We see that discontinuations for edema were less common than for hypertension. Numerically, etoricoxib was inferior to diclofenac for each pairwise comparison; although, some comparisons reached statistical significance.

Here is another table. This time accounting

for the numbers of patients who experienced CHF that resulted in hospitalization. As was previously stated for CHF, a retrospective adjudication procedure was conducted to confirm the cases. As expected, rates of CHF were lower than for edema. Again, the overall trend is that etoricoxib has higher rates of CHF than diclofenac.

Differences between etoricoxib and diclofenac for the renal laboratory abnormalities were not as marked. In certain groups such as the MEDAL, 90-milligram, OA population, there appeared to be excess toxicity associated with etoricoxib, although in most comparisons there was little difference between groups.

Again, we examined the non-MEDAL database for additional information. MEDAL did not include the dose of 30 milligrams, which is being considered for approval now, although the non-MEDAL database does. I must repeat the numbers of patients comprising these database are small by comparison to MEDAL.

Sample sizes for etoricoxib ranged from 220 at 90 milligrams to 1,014 at 30 milligrams. This

slide shows the rates of AEs related to hypertension and edema. These are not necessarily discontinuations, they are just reported as adverse events.

This is the placebo-controlled data set which truncates data at 12 weeks. The comparator groups include placebo, a wide range of etoricoxib, and three active comparators. For edema, there is not much difference in rates between the different doses and comparators. For hypertension, there appears to be dose response for the range of etoricoxib tested.

In the pertinent range, which of course is 30 and 60, the rates of hypertension appears similar to naproxen and ibuprofen; although, they may be higher than in celecoxib.

In this slide, we see the six-month and twelve-month active control populations, the six months is versus celecoxib and the 12-month is versus naproxen. Thirty milligrams of etoricoxib appears inferior to 200 of celecoxib for hypertension.

The relevant doses, again here are 30 and 60, of etoricoxib appear similar to naproxen except

for the 30 milligrams for edema where it might be inferior and the 60 milligrams for hypertension where it might be inferior.

To summarize the renovascular safety findings, etoricoxib 90 milligrams, causes hypertension, edema, and congestive heart failure than diclofenac. Etoricoxib, 60 milligrams, causes more hypertension and slightly more edema and CHF than diclofenac. Compared to other NSAID the relevant doses of etoricoxib appear mixed for renovascular safety.

As a class NSAID have been observed to have the potential to elevate LFTs. All trials included routine monitoring of serum chemistries including transaminases, alkaline phosphatase, and bilirubin. The Applicant recorded patients who discontinued for hepatic-related adverse events and similar to renovascular lab events predefined at threshold for elevations in transaminases that would be considered significant.

This table, which is identical in layout to those from the renovascular section showed the

discontinuations for hepatic-related events. In each comparison etoricoxib was superior to diclofenac.

To summarize our findings, etoricoxib is effective at 30 and 60 milligrams; although, there is weak evidence that there is a meaningful dose response between 30 and 60 milligrams.

For the cardiovascular thromboembolic event as assessed by relative risk, the pooled MEDAL data show comparable CV risk versus diclofenac. In addition, we note that the confidence intervals for the relative risk do not exclude one.

However, given the 95 percent confidence interval, the attributable risk for etoricoxib compared to diclofenac could be as high as 2,300 excess events per million patient-years at a dose of 60 milligrams. The non-MEDAL database suggests that etoricoxib is inferior to naproxen.

Etoricoxib causes more hypertension than diclofenac and slightly more CHF and edema. It was mixed for renovascular toxicity versus the other active comparators.

Etoricoxib was similar to diclofenac with

respect to medically significant upper-GI events; although, it was superior when nonclinically significant ulcerations are included.

That concludes my presentation.

CHAIRMAN TURK: Thank you, Dr. Shibuya.

Are there any clarifying questions for Dr. Shibuya?

Ms. Solonche.

MS. SOLONCHE: Yes. On Slide 16, I noticed it says on this slide Prescribed to 1 million patients." You said "1,000 patients."

DR. SHIBUYA: I'm sorry.

MS. SOLONCHE: I just wanted to check that. But here you say a million patients and later that is some reference to a million patient-years. Are these two different things or the same thing?

DR. SHIBUYA: I should have been more clear, and I'm sorry if I misspoke. The assumption for our attributable risk analysis was a million patients treated for a year.

MS. SOLONCHE: Okay. Thank you.

CHAIRMAN TURK: The next speaker will be

Dr. David Graham from the Office of Surveillance and Epidemiology at the FDA.

Dr. Graham.

AN EPIDEMIOLOGIC PERSPECTIVE ON ETORICOXIB

(PowerPoint presentation in progress.)

DR. GRAHAM: Good morning. Over the next 15 minutes or so, I would like to provide an epidemiologic perspective, a population perspective, to the issue of NSAID, cardiovascular safety, and gastrointestinal benefits. Because the decision ultimately that gets made regarding Arcoxia to etoricoxib is a population decision.

It's not a decision, well, are there some patients who can benefit, it's from a population perspective, is there a benefit that will exceed a risk.

Because understand that with any drug that is used, they are used far outside the labeled indication and they are not used in a sequential fashion. Because of the miracles of modern marketing, people will try the latest and the newest.

As an introduction what I would like to do,

these are the areas that I will go over in the course of my talk, I want to talk about what is known and not known about NSAID-related hospitalizations for upper-GI events and upper-GI mortality. I think there is a lot of misinformation or incorrect information or uncertain information that the Committee should be aware of.

Also, what is known about NSAID-related cardiovascular risk? You will see that there is a stark contrast in interpretation of the data between what I will show you and what the sponsor presented.

Another question I think you really have to consider is, is diclofenac a reasonable comparator for a drug that will be marketed to millions in the U.S., many with underlying cardiovascular disease.

Then, what is known about the performance of COX-2 selective coxibs compared to other therapies with respect to GI risk and cardiovascular risk? Here, I'm talking about proton-pump inhibitors.

Finally, based on the current state of knowledge should etoricoxib be approved. To begin with, there is a widely quoted figure in the

literature of 16,500 deaths due to upper-GI bleeding, and this was provided by Dr. Singh at Stanford based on a review of the ARAMIS database, which is a database of patients with osteoarthritis and rheumatoid arthritis.

In order to come up with that estimate of 16,500 deaths a years due to NSAID, he needed a case fatality rate of 17 percent. That is when you take the composite of these GI death rates, 22 percent and 11 percent. Overall, they needed a 17 percent death rate to get to that number.

Now, is the death rate for upper-GI complications 17 percent? Well, here is a study, it was a large population-based study, so it is not in basically a SISNeT based on referral centers. This is sort of a population-based center looking at hospitalizations and outcomes for upper-GI events

This was from the Province of Saskatchewan. You can see the years, and they predate the publication of the paper I showed earlier. The important to see is that overall the case fatality rate was about 5 percent. Okay, now that's back in

the 1990s.

I went to data from the National Center for Health Statistics to sort of look at, well, what's happening in the United States today. Online, available for the years 1999 to 2003, I was able to come up with this information.

What you can see is the number of hospitalized discharges for upper-GI ulcers, perforations, and bleeds, acute and chronic. These are the ICD 9 codes that we use and the ICD 10 codes that we use, an average of 332,000 per year over this 6-year period or 5-year period, an average of 4,700 deaths a year from these discharges, for a fatality rate of 1.4 percent.

What I would like to point out, that a case fatality rate of 1.4 percent is that that is all causes. This isn't just people on NSAID, this is people with H. pylori infection who get it with an ulcer, perforation, or a GI bleed and end up in the hospital, which is a substantial portion of what this 332,000 is.

I think that there is reason to question

whether that 16,500 number is really accurate or not. That then raises the question of, how big a public health problem is this in terms of morbidity and mortality?

I now want to turn next to what is known and not known about cardiovascular risk with NSAID. The sponsor presented a slide similar to this from the meta-analysis of clinical trials published in "BMJ" by Kearney, et al., late last year.

What I'm presenting here is the data from myocardial infarction. You can see the various COX-2 selective coxib NSAID. Overall, they have an increased relative risk of about 1.9.

The important thing is, though, all those very wide confidence intervals, that the point estimate for etoricoxib is sort of on the fringe. It's a small amount of data, but the suggestion is there that etoricoxib could theoretically be a worst coxib than the other coxibs that are currently marketed or rofecoxib that was previously marketed.

From that same study, looking at myocardial infarction with traditional NSAID, in this study the

problem -- well, it's not a problem but the way the studies were done traditional NSAID were compared to coxibs and then the relative risk estimates would come out.

What you see is that for naproxen the risk of naproxen is actually about .45. If we were going to say what's the risk of naproxen versus a coxib for myocardial infarction, the risk of naproxen is only 45 percent that of a coxib. In other words, this is sort of presenting in the reverse fashion, the naproxen is twofold or a little over twofold protective. In other words, naproxen has a much safer cardiovascular profile than other NSAID or than coxibs.

Now, this is a summary. The previous two slides were published meta-analyses of randomized clinical trails. This study from McGettigan and Henry published in "JAMA" about the same time as the other meta-analyses is published dealt with observational studies.

These are epidemiologic studies, so they don't have the benefit of randomization. What is done

instead is an attempt is made to adjust for those other risk factors.

Along the "X" axis we have the variety of NSAID that were included in this meta-analysis. The number in parentheses underneath is the number of studies that gave rise to the point estimate and the confidence interval.

The important take-home messages from this slide I think are that, one, diclofenac and observational studies clearly increases the risk of myocardial infarction, and in fact looks very similar to rofecoxib.

The second is that naproxen is neither cardioprotective nor cardio harmful. It is neutral with respect to cardiovascular risk. Now, ibuprofen had an elevated point estimate of about 1.1 but the 95 percent confidence interval included one.

Since the publication of that meta-analysis in November of last year, several other papers have come out that included information from observational studies reporting on the myocardial infarction risk of various NSAID, and so those data are included here and

they are color coded to match the particular paper that they are reported from.

Importantly, the relative risk for diclofenac in these additional two studies almost spot on with what was found in the previously shown meta-analysis. For naproxen, we have three studies, two that include the null and one that is a little bit above the null. If you redo the meta-analysis and include those in it, it basically just shifts the risk of naproxen from, like, .97 to .98. In other words, naproxen remains neutral.

Celecoxib may have a slight increase in risk. Etoricoxib from two published studies has a substantially increased point estimate but with very wide confidence intervals because the level of use in those studies was less than in other studies. With rofecoxib, we see the continued pattern of increased risk.

This slide now compares what we see from the meta-analyses of the observational studies in blue and the randomized clinical trials in red with respect to myocardial infarction risk for diclofenac, ibuprofen,

and naproxen.

The take-home message here is that it's incontrovertible, diclofenac increases cardiovascular risk. Likewise, incontrovertible, naproxen does not increase cardiovascular risk.

In this regard, FDA's blanket labeling of NSAID is incorrect, and I hope that they will look to change that because there is one NSAID on the market that does not increase cardiovascular risk, and that is, naproxen.

With ibuprofen, there is a suggestion that the risk could be increased and more study is needed. It's risks are probably, in my own estimation, intermediate between that of diclofenac and naproxen.

Okay. Now we have summarized the cardiovascular risk with NSAID. I want to look at the question of COX-2 selectivity of various NSAID because this ties in with diclofenac. This is a publication from Patrono, et al., in 2001. He is a very well-regarded researcher in the area of COX-2, COX-1, and aspirin actions.

What they have done here is looked at a

variety of different NSAID and their ratio of COX-1 to COX-2 inhibition. The closer to one that you are, the more neutral you are with respect to inhibiting both the COX-1 enzyme and the COX-2 enzyme.

The higher the number, the more likely you are, the stronger preference, predominance of effect, is a COX-2 inhibition. What we see here is that diclofenac is virtually identical to celecoxib with respect to its COX-2 selectivity.

This is from another publication by Gary Fitzgerald and Patrono, and it's showing similar data. Along the "X" axis we've got inhibition of COX-1 and along the "Y" axis inhibition of COX-2. If you are below ths line, you are predominantly COX-2 selective.

The further down below the line along this "Y" axis you are, the more COX-2 selective you are. What you should note is that diclofenac once again is about as COX-2 selective as celecoxib but not as COX-2 selective as rofecoxib. Naproxen and ibuprofen have a slight preference for COX-1 inhibition, but they are basically neutral.

Okay. Looking at diclofenac, is diclofenac an appropriate comparator for etoricoxib? Well, we have seen that it is COX-2 selective, so that would raise a question because most of the NSAID out there, the traditional NSAID, are not COX-2 selective.

What about in the U.S. market? We were told by the sponsor that diclofenac is the leading selling NSAID worldwide, and that's true. But in the United States, it is one of the least sold, least used NSAID.

In this slide, I'm using Verispan data, which is a computerized national database of drug use data that FDA has access to. We have plotted the percent of the NSAID market. We have grouped all the coxibs together: ibuprofen, naproxen, diclofenac, and all others.

What I would say is that this "all other" category, every NSAID in this category had use that was less than that of diclofenac. You're seeing the leading NSAID here. What you see is that overall about 35 or 36 percent of the market was coxibs, almost 25 percent was ibuprofen, and nearly 15 percent

naproxen, and less than 5 percent diclofenac.

Now, in the next slide, I show the same data but now I've taken the coxibs out of the picture so that you can see how do these traditional NSAID stack up against each other in terms of their share of the market.

What you see is that it's approaching 40 percent for ibuprofen, between 20 and 25 percent for naproxen, and 7 percent for diclofenac. For all of those other NSAID together, again, about 35 percent.

What we have is a situation where a clinical trial program has been developed and focused on a drug that is rarely used in the United States, and I would contend is not a relevant comparator for the U.S. market.

Now, diclofenac as a reference group, we've seen previously that diclofenac raises myocardial infarction risk, and we know from history that rofecoxib does as well. What's the value of a comparison between a coxib and diclofenac if what you're interested in is upper-GI cardiovascular risk?

Well, the answer is it has no value. This is a published study by the sponsor looking at rofecoxib versus diclofenac. You can see pharmacoepidemiology drug safety was published in November online. They found a hospitalized myocardial infarction risk of basically one, comparing rofecoxib to diclofenac.

Well, we already know that rofecoxib increases the risk of myocardial infarction. This is misleading in the sense that you might be led to believe that there is no cardiovascular risk with rofecoxib, but you know that there is.

Now, similarly, this was published in Lancet. This is looking from the MEDAL study and the APTC events, which hospitalized AMI would be a subset of this. This includes also nonfatal strokes and then cardiovascular fatal events. Once again, we get a relative risk versus diclofenac of about one. Should we be reassured? I think the answer to that is no.

I am focusing now on data from the non-MEDAL portion of the sponsors program. Dr. Shibuya presented these data in a slide that had a lot of

information on it, so I wanted to emphasize this particular piece of information because I think it's the most relevant information in everything that has been presented today about cardiovascular with etoricoxib.

What this shows us is that etoricoxib increases the risk of myocardial infarction with ATPC events, that is, myocardial infarction, stroke, and cardiovascular death. It increases the risk 2.7-fold compared to naproxen. As we showed before, naproxen is neutral with respect to cardiovascular risk.

Now we have reviewed cardiovascular risk. We have reviewed diclofenac as a comparator. I want to talk about what we know about combining traditional NSAID therapy with proton-pump inhibitors as an alternative means of treating for prevention of upper-gastrointestinal complications.

There are two published randomized-controlled clinical trials in the literature that have looked at that. In both of those studies, what has been found is that there is no difference between treatment with a traditional NSAID plus a PPI and a

COX-2 selective inhibitor or a coxib.

This study by Chan, et al., was published in "The New England Journal" in 2002. The basis study design was they collected a bunch of patients who had already had upper-GI bleeding from an ulcer, documented.

They were recovered and then they were randomized to receive either celecoxib or in this case diclofenac plus omeprazol, which is one of many proton-pump inhibitors.

What you can see is that over time there was really no difference in the risk of a recurrent upper-GI bleed in the two groups. The Log Rank test was .6, and that says that there really is no evidence of difference.

This followup slide is from that paper as well, and it shows the net difference in the probability of recurrent bleeding was 1.5 percent in favor of celecoxib but with very wide 95 percent confidence intervals. The conclusion was that there really is no demonstration of a difference in effect.

The second published clinical trial by Lai,

et al., in "The American Journal of Medicine" in 2005, followed a very similar study design. Patients who had already had one bleed from a documented gastric or duodenal ulcer who had recovered from that and then who were randomized to receive either celecoxib or in this case naproxen plus lansoprazole. Once again, what we can see over time is that there was no difference in the two groups, the Log Rank test was .37.

This slide shows the cumulative probability of recurrent ulcer bleeding and shows the difference between the two, and there was a difference of 2.6 percent favoring celecoxib but with wide confidence intervals that include the possibility that naproxen plus PPI were superior.

The accompanying editorial to this article stated that we have a real quandary because it appears that traditional NSAID plus a proton-pump inhibitor are as effective as COX-2 selective inhibitors in the prevention of serious upper-GI events.

I then went and reviewed the published literature for observational epidemiologic studies to

see could we gather some information there that might help inform this question of proton-pump inhibitors and do they help in the prevention of gastrointestinal bleeding if you're taking a traditional NSAID.

I found these seven studies, but two of studies reported results from the same, two papers reported results from the same study and so they are grouped together.

We have what the outcome was in each of these studies, the number of cases. This is the number or events of whatever that outcome was that were in these studies. They were all case-controlled studies.

Then, some of studies presented the results as an NSAID plus a PPI versus non-use of either, other studies presented the results as an NSAID plus a PPI versus an NSAID, and then there were some studies that presented the results both ways. In a way, then we can try to triangulate on what do we think the effect might be.

What we see is that, and we will go down the column of NSAID plus PPI use versus non-use, but what

we find is that basically in all of these studies we know from background work that traditional NSAID compared to non-use will increase the risk of upper-GI bleeding and hospitalization and ulceration by a factor of generally three- to fivefold.

You expect the relative risk for this column of somewhere in the three to five range. If you get something around one, what that is suggesting is that the proton-pump inhibitor has actually prevented the occurrence of those upper-GI complications. What we see in all of the studies basically is evidence of a protective effect of the proton-pump inhibitor.

Now, in studies that compared NSAID plus PPI versus an NSAID alone without the PPI, which in some ways is more satisfying, we find once again that there is generally a substantial reduction in risk of upper-GI complications in patients who received an NSAID plus a PPI versus a traditional NSAID. The point here is that if we are thinking from a population perspective of how to deal with an important public health problem, when we do clinical trials, is it reasonable to have an arm in the

clinical trial that does not include a traditional NSAID plus a PPI from the randomization on so that we don't have to try to sort of reconstruct things after the fact and maybe be confounding effects?

Is it ethical, since we know that NSAID without gastroprotection increase gastrointestinal risk, is it any longer ethical to conduct studies in which you don't offer gastroprotection in those studies? That's a question that I think the Committee should ponder.

Okay. We are getting close to wrapping up now. The Food Drug and Cosmetic Act, Section 505 states regarding the approval of a new drug:

"Adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested."

I have italicized "all methods reasonably applicable" because I want to question whether we have that, in fact, now.

The public health considerations I think are important. Cardiovascular disease is the leading

cause of mortality in the U.S. Earlier in the presentations, one of the members of the Committee asked the question, "What is the background rate of the patients who are going to likely be receiving this drug." Because there was some concern about patients, a heterogenous population of patients, at higher risk not maybe being included in the Etoricoxib Development Program.

Well, if you go to the American Heart Association, you can find the statistic that the background rate for AMI in males is 65 to 74, and that is pretty much the target population for etoricoxib or a big part of it, is 2 percent per year. That is one in 50 per year.

If you look back through all the material that you've gotten from the FDA and the company, what you will see is that the background rate in the MEDAL Study was about .5 percent versus 2 percent, even though their mean age in the study was 62. The MEDAL population was, in essence, a healthier population than the general population that's going to get this drug.

Now, what is the potential impact? Remember, we got that 2.72 for etoricoxib verus naproxen. Well, I've done some calculations where I calculated number needed to harm and then what would be the number of excess heart attack events that occurred as a result of using etoricoxib rather than naproxen in a population.

Now, a similar analysis was presented by Dr. Shibuya, but there he was comparing diclofenac and etoricoxib. If you remember, they looked the same with respect to cardiovascular disease, so you wouldn't expect to see much in the way of excess deaths.

Well, what we have here is that the potential impact of that relative risk is that for this target population of males 65 to 74 we would go from a risk of 1 in 50 per year for myocardial infarction to a risk of 1 in 18 per year. The number needed to harm is 147 person-years.

What that means is that for every 147 people I treat for one year I produce another case of myocardial infarction above and beyond what would have

occurred.

If we treated a million people for a year with etoricoxib, we would get 6,800 events. On the slides, it says "14,700" and you should change that. I made a mistake there, and so I want you to know that it's 6,800.

Now, that 6,800 and this number needed to harm are based on what we saw in the sponsors Non-MEDAL Development Program where in those population the background rate for heart attack was .4 percent, not 2 percent.

What happens when you have a higher background rate is that number jumps, so .4 percent versus 2 percent. Well, 2 percent is five times greater than the .4 percent. What that means is that the attributable risk would go up fivefold. Instead of 6,800, we would be talking about over 30,000 cases.

This is just to emphasize, we don't have great precision on these numbers, but what you're talking about is a potential public health disaster. The wider and more extensive the use of etoricoxib is in the general population, you will get a multiplier

effect, and you will get more cases occurring. Then, we could have a repeat of what we had with rofecoxib.

Now, not all NSAID are the same with respect to cardiovascular risk. That may be FDA's official position, but FDA is wrong, and there is ample evidence to show that they are wrong. They are wrong with respect to diclofenac; they are wrong with respect to naproxen.

In addition, naproxen does not interfere with the beneficial effects of aspirin, so if you're looking to see is there some advantage or not, naproxen doesn't interfere with aspirin use.

Further, traditional NSAID plus PPI appear to be equivalent to coxibs for upper-GI outcomes. We have randomized clinical trials data and epidemiologic data. There is no apparent or demonstrable added benefit to etoricoxib use that at least is apparent to me.

To conclude, diclofenac is an inappropriate comparator for the assessment of population cardiovascular risk. The drug is not used very widely in the United States; it's COX-2 selective and it

itself raises cardiovascular risk. The Applicant's program is based primarily on this inappropriate comparator.

Etoricoxib probably confers a substantial increase in cardiovascular risk, and this has enormous public health and population consequences. Etoricoxib is no more effective for pain relief than traditional NSAID and naproxen plus a PPI is equivalent to coxibs for gastroprotection.

It has the advantage of substantial cardiovascular safety, and it is substantially less expensive. Although that may not be a primary concern of this Committee, it is a concern for most patients. You can get generic PPI and generic NSAID for a fraction of the cost of what etoricoxib will be.

Secondly, going back now to the FD&C Act, approval should be based on adequate tests by all methods reasonably applicable.

Regarding demonstration of efficacy, I think that the current tests that are done are probably adequate. However, what I would emphasize is that there is no difference in pain relief between the 60-

and the 30-milligram dose. Why court disaster by approving a 60-milligram dose where we have substantial data that there are very high cardiovascular problems.

Now, regarding demonstration of safety, I want to point out to the Committee that there is basically no data on the safety of the 30-milligram strength, so what the company is asking you and asking FDA to do is blindly accept that the cardiovascular risk there isn't present.

We don't know that for a fact. In fact, there is every reason to believe that the cardiovascular risk with the 30 may be very close to what we saw for the 60 because the level of pain relief with these drugs is similar.

Now, current tests I believe for safety are not adequate or reasonable at this time. I would propose that a coxib such as etoricoxib, that it should be compared to naproxen plus a PPI for upper-GI outcomes and for cardiovascular outcomes.

In addition, I'm not showing it on the slide, but I would include a celecoxib arm in all

clinical trials. Celecoxib of all the coxibs that are marketed at a 200 milligram daily strength has the most data to suggest that its cardiovascular risks are probably minimal or nonexistent.

As we saw from the FDA presentation, celecoxib does not increase hypertension or edema and so it has a lot of advantages that I would expect, I would think, and the Committee might want to question, wouldn't you be looking for superiority or at least equivalence with respect to those before you go approving another COX-2 selective inhibitor?

Thank you very much.

CHAIRMAN TURK: Thank you, Dr. Graham.

I have time for just two burning questions from people.

DR. FRIES: Thank you, David. On your Slide 3, I just wanted to make a clarification, since that "16,500" number emanated from my shop. I've been ashamed of it since it came out.

DR. GRAHAM: I wasn't trying to embarrass you.

DR. FRIES: No, no, no, I'm not embarrassed

because I've told many people that that number was incredibly elevated. My number when we did the original assumptions was 7,500, not 16,500.

That number represented a 1992 peak of the epidemic extrapolation coming from rheumatoid arthritis patients where we could actually count things.

When we got into probable rheumatoid arthritis patients, as was done later, nobody knows how many of them there are. Nobody knows what the rates are because we haven't studied them with regard to our data.

The core data kernel was fine for 1992. We have published since then that with use of less toxic NSAID, excluding the COX-2 selective inhibitors, the counted incidence rates have gone down by a factor of three since that time, a big shift toward ibuprofen in lower dosage and, similarly, big changes in aspirin dosage going down, and some PPI use.

There has been a successful approach to this number. If we used our original extrapolation numbers, we would say about 2,500. I suspect that is

too high for GI deaths right now, but at least it gets you to a ballpark that's a lot closer.

DR. GRAHAM: Right. Well, thank you for that information.

CHAIRMAN TURK: Thank you for the clarification.

One more question, if there is one. Dr. Pasricha, you were I think slightly first.

DR. PASRICHA: Okay. Well, thank you.

CHAIRMAN TURK: Remember, there will be an opportunity to have questions after the lunch break when we come back.

DR. PASRICHA: Right. I think I would like to make an important clarification regarding the use of NSAID and PPI strategy. The data that you showed for Chan and the Lai study is treating the patient who has had a demonstrated GI bleed and to prevent ulcers from recurring, so this is secondary prophylaxis.

I think we need to distinguish that from a strategy in which we are taking patients who have not had a previous GI bleed and getting them on a nonsteroidal or a coxib for the first time.

Then, the value of using a PPI is very different because it's a huge population and the amount of PPI it's going to take to do primary prevention has still yet to be proven in terms of either its value or cost-effectiveness. I think we need to distinguish those two things as we go forward.

CHAIRMAN TURK: Did you want to comment?

DR. GRAHAM: No, I think that's a point that's well taken. But I think it then sort of begs the question of, how are we going to get that data? I think companies coming in to get approval for drugs such as etoricoxib are the perfect opportunity to actually test, to test that.

Because you can go to Kaiser or you can go to the Veterans Administration and see what the price is that they get for naproxen or ibuprofen or whatever the PPI is that they use, and I can tell you that, you know, it's probably under 50 cents a tablet.

If your question is, "Well, am I going to spend $3 or $4 a tablet to give a COX-2 selective NSAID versus 50 cents to give that," and the goal is primary prevention, well, what we would need to do I

would think would be to show that the COX-2 selective NSAID is actually superior to that other treatment.

DR. PASRICHA: No, I agree. What I'm saying is the data doesn't exist, and in fact there is emerging data to suggest that a widespread use of PPI for a large proportion of the population may have its own adverse risk including that of osteoporosis.

DR. GRAHAM: Right.

DR. PASRICHA: We need to be careful as to, you know, making sure that these strategies are very clear as to what the patient population is.

DR. GRAHAM: I agree, but it begins with acquiring the data. I guess what I'm suggesting to the Committee is you are in a position to make recommendations to FDA about what the appropriate design is for future studies.

What is the type of information that we critically need to answer the questions, the very questions you have. I don't have an answer to those questions, but I've tried to raise those concerns. We need that information.

I think the information we have says

something very clear about etoricoxib, but we have more general questions that I think speak to the more global issue of gastroprotection NSAID use.

Because osteoarthritis, rheumatoid arthritis and just general musculoskeletal pain is a big public health problem. Nobody likes to have pain. We need data. I agree with you.

CHAIRMAN TURK: I would like to take a break now for just 10 minutes, so if you can, be back by 11:45.

(Recess is taken.)

OPEN PUBLIC HEARING

CHAIRMAN TURK: The public believe in a transparent process for information gathering and decision making. To ensure such transparency, at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of

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Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationship. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

MS. CLIFFORD: Thank you. Our first speaker today is Dr. Egilman.

(PowerPoint presentation in progress.)

DR. EGILMAN: Thanks very much. Someone who controlling the slides anyhow.

I'm a physician and a clinical associate professor at Brown. That's not me (showing slide), but he is probably better looking than I am. That is me.

Some of this presentation is based on documents I have been able to access in my role as an expert witness in Vioxx litigation, so I titled it "Lessons from Vioxx."

I see that this is kind of like my wedding where, like, the groom's side and the wife's side. More important, though, just like my wedding, the analysts are in the back, okay. They would have been welcome at my wedding. Of course, they are the real audience. Because they are the people, rather than the patients, who are asking for this drug, unless they're short of course.

Since I'm in Washington, I know he couldn't be here but people are familiar with Dick Cheney. A lot of you thought that he was fat and ugly until you saw me. Of course, compared to me Dick Cheney is a handsome fellow, well dressed, and a good speaker, just like Arcoxia looks pretty good with diclofenac. Halle Berry is not going to be used for a comparator and hasn't been.

I would like to start by saying an additional Ronald Reagan quote, "Fool me once," as in

Vioxx, "shame on you. Fool me twice," as in Arcoxia, "shame on me."

COX-2s increase mortality overall. All the Vioxx studies have increased mortality or no difference in mortality. COX-2s may cause Alzheimer's. Safety data is unreliable.

I'm going to try to give you some examples from the Vioxx dataset on why that's true. Merck had delayed and I believe continues to delay, I know they continue to delay submission of even Vioxx-relevant data.

David stole some of my thunder here. The real question the public wants to know is, what's the best way to treat RA? Then, when we look at doing trials, one year placebo trials are unethical. Bombardier, who published Vioxx's VIGOR trial, had previously done a one-year placebo RA trial. They are not unethical.

On the other hand, the VIGOR trial, which was described by Dr. Skolnick of Merck as like testing Mevacor® for liver safety in patients with hepatitis, was unethical. The MEDAL trial may be, questionably,

unethical since both groups were put on drugs that lead to higher risk of heart disease.

Therefore, if you want to answer the questions, following up on David's last comments, long-term placebo trials sort of establish safety, and there is no excuse for not doing them.

As you saw from the FDA presentation, which the important question that wasn't asked before that you need to ask is, what's the number needed to harm or treat or help?

That needs to be applied to the entire patient -- not the stomach, not the left arm, the right arm, or the kidney, but the entire patient -- including the heart, et cetera.

In the case of Arcoxia, there is more hypertension, there are more renal complications, there is more CHF, there are more strokes, there are more MIs, and there are more arrhythmias.

Just a little comment, the atrial fib. data, I could be wrong, there is no data in the Merck document that indicates what the atrial fib. data is on 60 milligrams. It just says that it's

"comparable."

My suspicion, based on my review of the way these presentations have been given in the past, is that that means that there are more events on Arcoxia, but it's just not statistically significant. I could be fooled. Maybe we'll find out later now that I ask the question.

Let's look at deaths. In the Vioxx trials, there were always more deaths on Vioxx than on the comparators. The reason for that is COX-2 is needed for healing of GI ulcers. What's the comparative death data not for diclofenac, that's GI bleed deaths, which is kind of an important GI effect.

I haven't heard that number. I'm curious about that number. It seems like a number that one might want to talk about. It was never talked about with Vioxx. There is data showing comparability in some of the MEDAL trials, but I would like to see the numbers in all the trials overall.

It is not true that CHF was adjudicated similarly to the other events. CHF was deleted from the list of events to be adjudicated by Merck post hoc

in October, October 3, 1999. The decision was made December 29, 1999, and it was crossed off.

Atrial fibrillation was an event that was supposed to be sent for adjudication in the original SOP. It also was deleted December 29, 1999, retroactive to October 3, 1999.

In the case of CHF, for these trials different methods were used to adjudicate them. In some cases, the case of the EDGE trials, the trials were frozen and one case published, and then they went back and got the data for CHF in that trial.

These are important I know small, potential details about how data is acquired and achieved, and certainly it leads me to question whether that data is reliable.

More deaths on COX-2. Perhaps, the best example of that is the large AD trial, 1,400 patients or so, Thal, et al., published. Merck claimed that it wasn't a problem because there was no pattern of death.

Well, there was a pattern of death. The excess deaths were all caused because of COX-2

blocking. COX-2 is part of the response to pneumonia. There were five deaths from pneumonia in the AD trial, zero in the control group.

There were GI bleed deaths in excess. GI bleeds get worse if you block COX-2. Then, of course there was almost a two-to-one rate in increased rate of conversion to Alzheimer's disease for people on Vioxx.

There was an increased death rate from accidents, many of whom it was suggested may have actually died from sudden death, but they may have died from accidents. If you cause people to develop Alzheimer's disease, you will cause people to die more often of accidents.

These are real effects. This effect was duplicated in another trial, a smaller trial by Aisen, A-I-S-E-N, not statistically significant but close. The same drug, Vioxx, increased rates of Alzheimer's disease. The theory was it was going to go the other way, it didn't.

You need a death warning if you're going to approve this drug, that is, people have been shown to

die more often if they take COX-2s and COX-2s may cause Alzheimer's disease.

This trial, the AD trial, another ethics comment, the AD trial would have been stopped but there was a planned DSMB which Merck stopped even though there was a two-to-one rate of increased conversion and a two-to-one rate of increase in mortality, both of which were statistically significant and evident within the trial within a year into the trial.

AD warning needed on the label for Arcoxia, if you're going to approve it. It's a class effect. No one has spoken about this. It hasn't been looked at, but it's there.

Now, let's look at Merck and its safety. If we're going to rely on their data, let's look at how it gets done.

In general, the horse is supposed to be in front of the cart. You follow the SOP. You don't do things and then write the SOP. Not exactly. The 14-day cutoff for considering cardiovascular mortality was not in the original SOP.

It was, in fact, chosen after they knew the results of the VIGOR trial. It was questioned by Dr. Shapiro, the Merck statistician, as being inappropriate because CV mortality should be evaluated in an ITT format. They didn't do that, and they continue to not do that.

Here is the cross-off sheet. You thought I made this up. Twenty-one are events, a complicated document. You will see three dates on the document. The top, right-hand corner is when the changes were made. The cross-outs are the events that were eventually in the SOP that were then deleted from the SOP, and then did not go to adjudication.

The top, right arrow is "CHF" and "pulmonary edema" is another. The left arrow is "atrial fibrillation." It was not sent for adjudication even though you and I learned in the third year of medical school that CHF could be an MI, could cause an MI or be the result of an MI.

By the way, the changes were made one week after the DSMB told Merck that they wanted to look at a specific analysis of CV events from this trial.

They were postdated to October 3 because that was the first time unblinded data was available, I think.

Now, this is one of the examples of rewriting the SOP. This is from 2003. They are trying to figure out what they were actually doing, and they are writing the SOP after they have made the changes.

Here are some examples of some of the published revisions to the SOP. To quote Shakespeare in Hamlet, "It was not followed in the observance but in the breach."

Here is the document where they deleted "CHF" and they explained that they also didn't have a -- the definitions for CHF that have been mentioned here already, and that's partly because of this problem they readded CFH in as an adjudicable event in 2005, December 2005, kind of sort of.

I'm not exactly sure when it was readded, but it was readded in post hoc so that the data collection over the course of the trial was variable with respect to this effect and the other effects.

Here we have some cheating on some of the

adjudications. This is an example from AN-158, from the Alzheimer's trial. Two of the three external adjudicators said it was a sudden death or unknown cause, either one of which would have qualified for an APTC event. Sudden death would have been, of course, a cardiac event.

There was an internal adjudication, not in the SOP. You won't find it; but, yes, it's there. The internal adjudicator, in this case Dr. Barr, said it was an unknown cause of death. It was reported to the FDA as insufficient data to adjudicate the patient was on Vioxx. This case is not in the cases. It was a death.

By the way, the deaths were one off patientwise from becoming statistically significant in the data that went in the label, and this would have been an additional death that would have gone in the label that may have made the data statistically significant. One can make a difference. Every once in a while it can be the straw that breaks the drug's back.

In general, the Merck adjudication process

loses more Vioxx cases than placebo cases, and it's happened study after study. It was reported with respect to Arcoxia in the 2005 report. There were more Arcoxia events, it was 9 to 1, I think, that were found not to be confirmed CV events compared to the controls.

This is an example from the Vioxx Alzheimer's trial. The Vioxx cases were statistically significantly less likely to be confirmed if you were on Vioxx in 1998 to 2000.

The cutoff for data that went into it, because it was interim data that went in the label, was through March 16, 2001. Overall, it was not statistically significant; but, after all, the label didn't change. The data went in, and the deed was done.

Again, emphasizing what has been said before -- now you can go to the video -- you will see that the hundred thousand hospitalization data which Merck put in their document, on page 23, in this presentation for you they know it's not right.

Can you go to the film, please? Dr. Laine.

(Staff complies.)

(Showing video presentation.)

A VOICE: "Let's just take another quick crack--"

A VOICE: "At the hospitalizations."

A VOICE: "--at the hospitalizations for the VIGOR, all right."

DR. LAINE: "The reasons I actually think is because those numbers, by the way, that people use are totally incorrect and they are based on just extreme, totally incorrect data."

A VOICE: (Inaudible.)

DR. LAINE: "No everybody uses them because they sound good. No, they sound good. But, I mean, well, it's the same person that keeps putting them out. I mean, I have recalculated them also.

"So the only way you can do it is subtract those who do from those who don't, and that number doesn't take it into account. So to say it's due to NSAID is also incorrect.

"So there's about five different reasons why those numbers are totally bogus. But I agree, it's

out there in the common realm, and everybody uses those numbers. Yeah, because it's a very impressive sound byte."

A VOICE: "Does it help that when you're using a word associated with NSAID, does that sort water it down a little bit?"

DR. LAINE: "No. I mean, because the issue is -- part of the issue is you just don't have any idea. I'm not saying it's actually wrong, but the death rate is probably wrong. The hospitalizations problem may be right, just the death rate is probably wrong. But anyway, but as long as we say it's 'estimated' or 'reported' it's not me saying it."

A VOICE: "Right, right, okay."

(End of video presentation.)

DR. EGILMAN: It wasn't him saying it when this was recorded and placed in a video news release, these are the outtakes, and used and distributed to television stations all over the country because he said "It's been estimated"?

It was his words; it was his mouth; it was Merck marketing. Merck in their documents tell you

that they are very honest and comprehensively follow all FDA rules in marketing.

They have given you bogus numbers in your presentation right in front of you, and the bogus numbers are said to be bogus not by me but by Dr. Laine, who is in the corner over there.

Next, how do they present their data in published papers? Take it away, Dr. Laine.

(Showing video presentation.)

A VOICE: "How about renal findings in this study?"

DR. LAINE: "Well, that's actually not going to be -- I mean, the only thing that's in 'The New England Journal' article says that there is no difference in renal failure or renal dysfunction."

A VOICE: "Okay."

DR. LAINE: "So I don't think you really want to go there, do you, because there are no data on blood pressure or edema in the study. And the only thing it says specifically, and we were cagey about this, was related to renal failure, renal dysfunction."

A VOICE: "Yeah, and that's not what we're looking at."

DR. LAINE: "And that's not what you're looking at."

A VOICE: "Right."

DR. LAINE: "So, I mean, I would actually take that out because I think you don't -- no, I mean, I would just suggest that anything you do -- just as an aside, I'm set to leave in about an hour -- but you don't want to talk about that. Because if you start bringing up hypertension and edema, it's no where in the study."

A VOICE: "Right."

DR. LAINE: "So if you bring it up, it's not what's in the article."

A VOICE: "I agree. I agree."

DR. LAINE: "Okay."

(End of video presentation.)

DR. EGILMAN: Okay. It's true it wasn't in the study, but it was in the published paper. In your handouts there that I have, you will see what they were "cagey" about because I've summarized there the

renal and CHF and edema findings from the study that were "cagily," not my word, omitted from the VIGOR paper.

I ask you to look at the data hard, not just the way you've been presented, but you need to look at the underlying data. Unless you do so, you are making decisions in the dark with people who are willing to repeat bogus numbers to you over and over again at meetings like this.

MS. CLIFFORD: Thank you, Dr. Egilman.

Our next speaker is Sid Wolfe.

(PowerPoint presentation in progress.)

DR. WOLFE: Thank you for the opportunity of appearing here. I have no financial conflicts of interest.

Next slide, please. You're going to do it, or do you want me to do it?

(Staff complies.)

DR. WOLFE: The consideration for approval of etoricoxib or any other drug in this family involves three outcome variables: relative efficacy for osteoarthritis, relative cardiovascular risk, and

relative gastrointestinal toxicity, specifically the complicated cases such as perforations, bleeds, obstructions, and so forth.

The second variable is relative cardiovascular risk. In a recently published paper in "The New England Journal" by Bruce Psaty and Noel Weiss on the choice of comparator drugs, now you've heard about this but I think it's important to say what they said, which is: "Sponsors need incentives to evaluate drugs in a manner that highlights potential clinical value, not marketing potential."

They point out that the COX-2 inhibitors are associated with an increased risk of vascular events but they illustrate the importance of the issue of the choice of comparator by reviewing clinical trials of naproxen and, separately, diclofenac and they state: "These data suggest that as compared with naproxen, diclofenac," this is just compared with the two drugs, "diclofenac may increase the risk of vascular events by about 70 percent."

When you do a trial using diclofenac instead

of naproxen, right off the bat you're increasing the cardiovascular risks in the original group and, as you've heard this morning, make it more difficult to see whether there is a difference with the experimental group.

Just a minute on efficacy, and these are Merck's own conclusions. You heard them today. The point is that once daily treatment with etoricoxib at 60 is the same as naproxen, 500, twice a day; or diclofenac, 100 milligrams or 50 milligrams, three times a day; and at the 30-milligram the same kind of comparisons exist. That's an easy comparison.

There is no evidence whatsoever in terms of what we would think the most important thing, efficacy in terms of relieving pain, no advantage of this drug over a variety of other drugs, including ones available over the counter.

Again, you saw a piece of this in Dr. Graham's presentation. This is the very well-done meta-analysis by Kearney published in the "British Medical Journal" last year.

What you can see, these are just the COX-2

inhibitors. What you can see is that overall for myocardial infarction, the group of them with small numbers in this chart for etoricoxib but larger numbers later, the group of them had a 1.6, 8.6 increased risk of heart attack compared with a placebo.

They went on then to look at COX-2 drugs versus older NSAID. Again, this is a chart that Dr. Graham showed. I didn't realize it because I hadn't seen his presentation when I made this.

Again, at the top you've got naproxen being, in comparison with the COX-2s, essentially half as dangerous. Or, the COX-2s, conversely, have twice the risk of cardiovascular events as naproxen does.

What you can see is that for any NSAID it's less than that. For diclofenac -- it's any non-naproxen NSAID, which is mainly dominated by diclofenac -- it's much less, much less protection, in fact increased risk.

This is another way of looking at the data in this extraordinarily well-done meta-analysis. There was a paper published several weeks ago in

"Circulation" recommendations from the American Heart Association, which, by the way, concluded that for anyone with any cardiovascular risk or cardiovascular disease the drug of choice was naproxen.

They had an inverted pyramid as many of you may have seen. The last-choice drugs were the COX-2 inhibitors. What you can see here is that compared in terms of cardiovascular risk, naproxen has about the same cardiovascular risk as a placebo and the other older nonsteroidal inflammatory drugs have a higher risk including diclofenac, which is statistically significant compared with a placebo.

This is also from the American Heart Association paper comparing the odds of vascular events in randomized trials of COX-2 drugs in which naproxen is the comparator with those in which another non-naproxen NSAID, primarily diclofenac, is the comparator.

The relative risk of naproxen compared with the COX-2 drugs was .64, the relative risk of non-naproxen NSAID was 1.14, not significantly different from the COX-2 drugs, if you omit naproxen.

Thus, it's clear from all these analyses that the choice of the comparator, especially from the perspective of cardiovascular risk, makes a world of difference.

Although Merck has said, and you heard them say it this morning, that the choice of diclofenac as the comparator for etoricoxib for the MEDAL Study was strongly related to the fact that it's the most prescribed NSAID in the rest of the world. As you saw in Dr. Graham's presentation, that is certainly not the case here. It is one of the least prescribed drugs.

Since it's approved unfortunately, and I'll talk about that later, in the rest of the world and not here, it doesn't make a lot of sense to use that as a basis for choosing this.

Look at earlier pre-MEDAL studies in etoricoxib was compared to naproxen, this is before the MEDAL studies, suggest another reason why Merck might have chosen diclofenac this time. The following slides are from an FDA presentation at the meeting of this Committee in February of 2005.

This is what was submitted with the NDA at that time, rates per hundred years, hundred patient-years. What you can see is that for all the studies submitted as part of the NDA, etoricoxib had a much more unfavorable comparison with naproxen than with the non-naproxen NSAID. The thrombotic cardiovascular deaths occurred at a rate of .12 with naproxen but .22 with etoricoxib.

The next slide is more from this presentation by the FDA over two years ago, which the relative risk of confirmed thrombotic CV serious adverse events with etoricoxib is 1.7 times higher than with naproxen but only .83 times as high compared with the other non-naproxen NSAID.

The next slide shows the categories within thrombotic cardiac events, including MI fatal. For some reason, the blank spaces are, respectively: MI, fatal MI, sudden death, unstable angina, as well as the strokes on the bottom.

What you can see is that when you break down these thrombotic events it's pretty much higher for most of them for etoricoxib compared with naproxen.

The earlier EDGE study also used the comparison with diclofenac. As seen in the next slide, found a marked increase, more than twofold, in significant hypertension in patients using etoricoxib. You have seen that in this study, but this is another nonthrombotic kind of event but one, as Dr. Graham pointed out, that proposes a huge risk for subsequent cardiovascular events.

What you see is that there was more than a twofold increase in significant hypertension, "significant" being diastolic, over 110; or systolic, over 180 in the people using etoricoxib compared with diclofenac.

The next slide, again, from the FDA presentation, increased cardiac risk even in comparison with diclofenac can be seen on the next slide in which there is more than a twofold increase in heart failure in patients getting etoricoxib.

The summary is interesting in view of what we know about Vioxx. The summary, the FDA summary, is etoricoxib trends worse in terms of cardiovascular thromboembolic events, particularly cardiac MI.

Comparisons of etoricoxib to naproxen for these events are similar to rofecoxib, or Vioxx, naproxen comparisons, trial designs' concerns in EDGE II. Those were the choice of the comparison, comparator drug.

Confirming the "wisdom" of Merck's choice of diclofenac as the comparator for the MEDAL Study are the results as shown in the FDA presentation from this meeting, this slide that you are seeing now.

As predicted from the comparisons between diclofenac with its own increased cardiac risk and other COX-2 inhibitors, there is no significant difference in the confirmed APTC endpoint between etoricoxib and diclofenac.

The presentation you heard from the FDA was that it might be as high as 2,000 per million extra cases per million people per year, that the average was about 400, that's in excess. It is no where near the excess you would have seen with etoricoxib had this study been designed using naproxen.

Even though the increase in thrombotic events did not show up very much because diclofenac

was the comparator, there was clearly an increase in patients discontinuing because of hypertension-related adverse events. You have seen this in the presentation by the FDA. At either the 60- or 90-milligram doses of etoricoxib significantly more patients had to discontinue the drug.

Finally, in the case of serious gastrointestinal toxicity there was no benefit to etoricoxib compared with diclofenac as shown on the next slide. The rate of serious confirmed GI events with etoricoxib was .3 per hundred patient-years versus .32 with diclofenac, not significantly different.

I just want to comment at this point that I think this study was unethical because it followed the knowledge that naproxen had a much lower cardiovascular risk, via the VIGOR study done by the same company, than the COX-2 drugs. This is a minor variation, as I'll show on this slide, of Vioxx.

The next slide, again this was an elegant presentation of the numbers that were shown in other slides, was presented at the Advisory Committee

