hypersensitivity reactions and additional safety information.

[Slide]

Over 4,000 subjects were exposed to febuxostat at doses of 10 mg to 300 mg. The greatest exposure was to febuxostat 40 mg, 80 mg and 120 mg. The subjects enrolled were representative of a gout population with multiple cardiovascular comorbidities and risk factors. Greater than 50 percent of our population had renal impairment. We have long-term follow-up and we have well characterized the safety profile of febuxostat.

[Slide]

The safety dose groups will be as follows: For the Phase 3 randomized-controlled studies, APEX, FACT and CONFIRMS, the results will be given in percent of subjects. For the long-term studies, Phase 2 FOCUS and Phase 3 EXCEL, results will be given in 100 patient-years.

[Slide]

For the exposure of the Phase 3 randomized-controlled the mean exposure is given in days and, as you will note in the middle row are similar across the treatment groups.

[Slide]

However, when you look at the long-term studies, the patient-year exposure that is highlighted is different. This is primarily due to the study design in the EXCEL trial. I will draw your attention to the 80 mg dose group, having approximately 10 times more exposure than the allopurinol does group. If you look at the total exposure for febuxostat, that is approximately 15.5 times the exposure of the allopurinol dose group. Please keep these in mind when we are reviewing the information.

[Slide]

With regards to discontinuation, the total discontinuations across treatment groups were similar, but we note higher rates in the 120 mg and in the 240 mg dose group of 32.1 and 35.8 percent. If we look at the reasons for discontinuations and we look at gout flare, what you will note is that there were higher levels of gout flares noted in those two dose groups which are primarily driven by increase in treatment initiated flares. With regards to adverse events leading to discontinuations, I will discuss that in an upcoming slide.

[Slide]

For our treatment emergent adverse events, the total were similar across the dose groups for placebo,

febuxostat and allopurinol. The most common adverse events were upper respiratory tract infection; musculoskeletal and connective tissues signs and symptoms; and diarrhea. I will draw your attention to the diarrhea where we have a higher percentage of subjects who had diarrhea in the 240 mg dose group, which was a safety dose, with a large amount of treatment initiated gout flare and increased use of colchicine.

[Slide]

With regards to treatment-emergent serious adverse events, for the active groups between febuxostat and allopurinol we see similar rates along the top row. The most common of these serious adverse events, although low in frequency, were ischemic coronary artery disorders; pain and discomfort; heart failure; coronary artery disorders. The cardiovascular events will be reviewed in the cardiovascular safety discussion that Dr. White will present. The other events, as noted here, are primarily in the GI system and are also very low in frequency.

[Slide]

Treatment-emergent adverse events leading to discontinuationB-when we look across the treatment groups, when we look at placebo, febuxostat and allopurinol they are

similar, with some of the higher rates noted in the 240 mg group, with diarrhea, nausea and vomiting and neurologic signs and symptoms. All of these subjects were on colchicine.

The liver function analyses I will discuss more in the hepatic section. However, these subjects who had discontinuations due to liver function analyses, which is an adverse event term, when evaluated, the transaminase levels causing discontinuation was primarily driven by low levels of transaminase elevations, less than 3 times the upper limit level of normal.

[Slide]

In the randomized-controlled trial all-cause mortality the various causes of death are listed on this side, and when we look at the total rates of febuxostat compared to allopurinol, we see a similar rate of 0.22 percent versus 0.23 percent for allopurinol.

[Slide]

The summary for the treatment-emergent adverse events, serious adverse events and discontinuations in the long-term studies show that these incidence rates for these did not increase over time. We saw that the type of events in these long-term studies were similar to those in the

Phase 3 randomized-controlled trials. For discontinuations due to adverse events we did not see a trend based on timing or type of events.

[Slide]

When we look at all-cause mortality, this is the randomized-controlled trials and also the long-term studies, the randomized-controlled trials are now given by patient-year exposure to be able to look at that compared to the long-term studies. So, this is similar to what is presented a couple of slides previously. The rates, again, are similar, 0.45 for patient-year exposure and 0.45. For febuxostat in the long-term trial the rate is 0.38. The long-term trial includes studies up to 5 years in duration.

Now I would like to ask Dr. William White to present on cardiovascular safety.

Evaluation of Adjudicated Cardiovascular Events in the Febuxostat Program

DR. WHITE: Thank you very much. Good morning, everybody.

[Slide]

I am William White. I am professor of medicine at the Cardiology Center at the University of Connecticut, a

small public university in New England. I have worked there about 30 years. I have a long interest in the cardiovascular safety of non-cardiac drugs, including the arthritis therapies such as NSAIDS and COX-2 inhibitors, and I was chairman of the cardiovascular adjudication committee for the CONFIRM study and also retrospectively analyzed the cardiovascular events for the APEX and FOCUS studies.

[Slide]

As you have heard, there was concern in the initial application for this drug for the two clinical trials that were conducted, APEX and FOCUS, having about 1,700 patients in which there were more cardiovascular events that, in fact was adjudicated to be APTC such events, versus allopurinol. Due to this apparent difference the sponsor was asked to conduct more research with febuxostat.

[Slide]

So, I am going to actually review more than that. I am going to look at some of the non-clinical safety findings for this drug. I wanted to show you some evaluation of some cardiovascular risk factors that we have just performed on the Phase 3 clinical trial data; remind you of the cardiovascular burden in this particular sample

that is contrasted to other databases; review our blinded adjudication process, which I think satisfies most of Dr. Packer's concerns that he gave in his talk earlier today; and give you the results of the adjudicated events, which we refer to as APTC and non-APTC events, which I will describe in just a moment.

[Slide]

So, first of all, from the basic data, xanthine oxidase inhibition was not known to cause any cardiovascular averse effects. A number of non-clinical studies have been performed that identified no biological mechanism for any potential cardiovascular adverse effect.

This included in vitro studies which showed no deleterious effect on various cardiac ion channels and action-potential parameters. There was no evidence that febuxostat caused any significant effects on coagulation factors or platelet function. In a variety of models there was no evidence of a detrimental effect in animal models of hypertension, metabolic syndrome, heart failure, MI, myocardial hypertrophy and chronic renal disorders.

[Slide]

Now, one of the things we do get a little concerned about nowadays with non-cardiac drugs is if they

do things like destabilize blood pressure, or antagonize the lipoproteins, or perhaps make patients glucose intolerant, or make them gain weight.

[Slide]

So, we evaluated this in the Phase 3 clinical trial program, and I can tell you that there are no effects observed on blood pressure, blood sugar, lipids and weight.

[Slide]

Now, to look at blood pressure first from the Phase 3 controlled studies, noting that this is the proportion of subjects with this particular change from baseline from end of treatment versus baseline in the clinical trials, with febuxostat in red, allopurinol in green, the proportion of patients who were lower, the same or higher were quite similar for febuxostat across all doses as for allopurinol. The mean change is at the bottom of the slide. It is about 0.5 mmHg for systolic pressure changes in this large population.

[Slide]

For the total cholesterol, interestingly, I cut the bins in 10 so maybe that is why it looks non-normally distributed because I wanted to keep the parameters similar.

But we do see a few patients who actually had a lower cholesterol at the end of treatment compared to baseline and a few that had more. But, all in all, it was about a 1 mg/dL drop on febuxostat and a 6 mg/dL drop on allopurinol.

[Slide]

For blood sugar, again, there are no real differences between the two treatment groups for the distribution of changes from baseline. The mean changes were less than 1 mg/dL in 2,549 patients treated febuxostat and 1,200 with allopurinol.

[Slide]

Finally, looking at body weight, this is good, old fashioned body weight in pounds not body mass index, these patients started out with a fairly large body weight, averaging about 240 lbs. This is 95 percent men. And, they had really no significant changes in weight, a little lower on febuxostat relative to allopurinol, but not of much clinical significance to that.

[Slide]

Now, we have heard from both rheumatologists that spoke earlier today that patients or individuals with gout have a higher cardiovascular burden than patients who do not

have gout. That appears to be borne out by the two most recent publications in this area.

A prospective cohort study of over 50,000 male health professionals were followed up for more than 10 years for 500,000 person-years of assessment, and the good old MRFIT study, which was conducted in the 1970s and was a randomized clinical trial of specialized care versus usual care in a fairly high risk population of men with hypertension, and so forth, had 15,000 person-years of observation in the clinical trial and 80,000 if you include the extension up to 17 years of observation.

So, individuals with gout in the healthier population had an MI rate of 0.46 per 1,000 person-years of observation versus no gout 0.24, and CV deaths and all-cause deaths were also increased. You will note that in the less healthy population it was higher, as would have been expected. This was in an era when we were not treating patients with statins because they did not exist and we were not aggressive with other forms with renin-angiotensin blocking drugs.

[Slide]

So, we wanted to examine our population from the febuxostat database and that, of course, includes patients

on allopurinol. It is all patients together. The patients were, in fact, laden with cardiovascular problems. This is I think fairly representative of this disease. Our committee was very impressed by the number of comorbidities that these patients had. As you heard, about half were hypertensive. Many of them had dyslipedmia, defined either by diagnosis or by treatment with statins. And, there was a great deal, a great deal of obesity in this population, many of the patients having body weights over 300 lbs when they entered the study.

So, if we examine the cardiovascular burden, almost 90 percent of the patients had at least one cardiovascular diagnosis, that is, a prior history of atherosclerotic disease, an MI, a stroke or a major cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, obesity or smoking. Twenty-five percent of the patients had 3-4 such diagnoses or risk factors, and 5 percent had 5 or more.

So, I think the population that we have in our database here is consistent with what was observed earlier, that this is not a very healthy group of men, 94 percent men.

[Slide]

The CONFIRM study is the new clinical trial that has been conducted in response to the concerns that occurred in 2005 with the earlier application for febuxostat. It was, as you heard, a study involving 2,269 randomized patients to either 40 mg of febuxostat, 80 mg or allopurinol in which the dose was affected by level of renal dysfunction.

In this study there was a prospectively designed case report form to capture cardiovascular history at baseline, so perhaps better defined than in the earlier Phase 3 trials. It included a prospective evaluation of cardiovascular events. These cardiovascular events were defined in the study protocol.

We supplied the investigators at their sites and the coordinators with a cardiovascular worksheet to ensure that we would collect essential information. This had a checkbox but it also had places to write narrative information about their impression of the cardiovascular event. Then, we had a blinded adjudication of potential cardiovascular events that was performed by an independent committee, which In will describe in just a moment.

[Slide]

We defined before the study got underway a

cardiovascular composite, known as the Antiplatelet Trialists' Collaboration endpoint which most of you, I am sure, have become familiar with. We also had another group of major cardiovascular events that didn't fit into the APTC categories to utilize as another source for documentation of potential CV signal.

These endpoints have been used for a long time to evaluate cardiovascular safety, not only of cardiovascular drugs but also non-cardiovascular drugs, including antiplatelet drugs which, I guess, some people might characterize as a cardiac drug, and arthritis therapies, including nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and now xanthine oxidase inhibitors. So, we have a frame of reference for this particular category.

[Slide]

Here is the list. The APTC endpoints are cardiovascular death and nonfatal MI and nonfatal stroke. The non-APTC endpoints that we adjudicated were arrhythmias where there was not evidence of ischemia inducing the arrhythmia so that included atrial and ventricular, of course; various venous and peripheral arterial vascular thrombotic events that included pulmonary embolism, TPS thrombosis, arterial embolism, arterial thromboses;

hospitalized nonfatal congestive heart failure which included acute coronary syndromes, coronary revascularization, both percutaneous intervention and CABG; transient ischemic attacks which were hospitalized; cerebral revascularization which included carotid enterectomies, carotid stenting and other intracranial procedures if they were performed.

When it didn't meet those criteria we even had an Aother@ category which we considered a treatment-emergent cardiovascular event, such as severe hypertension that was de novo and required emergent treatment or hospitalization, cardiac syncope and things of that nature.

[Slide]

So this adjudication process was conducted in two phases in time. Prior to 2006 it was done retrospectively at the request of the sponsor to me based on their negotiations and discussion with FDA. This included an evaluation of all cardiovascular events that occurred in the two clinical trials and the extensions. I will tell you that I was not aware of the outcomes of these clinical trials. I know that was a concern of Dr. Packer. I understand that but, yes, I must have known there was a reason to be doing these but In had no idea what the

outcomes were between febuxostat and comparator drugs, including placebo. We used definitions of APTC and non-APTC endpoints based on the literature.

Now, in the new study, CONFIRMS, there was a cardiovascular endpoint committee put together and we developed a charter in which we defined our events, as I mentioned already, prospectively and categorized them in the charter before our process got under way.

[Slide]

These are the characteristics of the patients in CONFIRMS, 40 mg, 80 mg and allopurinol. They averaged about 53 years of age. These patients weighed about 225-230 lbs. Their blood pressures were 131/81. CholesterolsB-these are random cholesterols, were about 205; triglycerides about 250; blood sugars in the 108 range.

Many of these patients were taking concomitant medications of a cardiovascular nature, and this was pretty well balanced among the three treatment groups for aspirin, renin-angiotensin blocking drugs, drugs to treat diabetes, beta blockers and statins. I also wanted to point out that about 40 percent of the patients in the studies were taking NSAIDS.

[Slide]

This is disposition of the events. In the CONFIRM study 327 events were identified as potential cardiovascular events, including about 50 which were of a serious nature in 241 subjects. After this information was obtained it was adjudicated blinded to treatment group by the committee by each member independently. After they completed their work the information was submitted to me as the chair. I looked for corroboration among the committee members. When it existed, that was the defined event. When it did not exist we had a meeting to discuss the case in detail and come up with a final diagnosis.

As you can see, there were some events that occurred during screening. These were not counted in the final tally that I am going to show you in the results in just a minute. I just wanted to point that out.

There were 6 events defined as APTC in 6 subjects. There were 49 cardiovascular events of the non-APTC variety in 26 subjects. There were 198 events in 152 subjects which were defined or diagnosed as non-cardiovascular. In 13 subjects in which there were 18 events we found the data inadequate to come up with a final diagnosis.

[Slide]

Examining that group, all of these subjects were

not considered serious enough to hospitalize. Hence, that led to the poor level of data, as Dr. Packer mentioned occurs in some of these adjudication processes. However, the number of these cases were balanced among the 3 treatment groups, 4, 4 and 5 actually, and only one individual discontinued the study medication in each of those 3 treatment groups. So, we had 10 patients who continued in the study and we could follow and none of those individuals had an APTC event or a non-APTC event.

[Slide]

Let's now turn our attention to the results of this study. The adjudicated APTC events are shown here. In the febuxostat 40 mg arm there were no cardiovascular events of the APTC definition. There were 3 events in the 80 mg arm, at 0.4 percent, and 3 in the allopurinol arm, at 014 percent. There were no deaths on febuxostat during the CONFIRMS study. There were 2 deaths on allopurinol during this trial. One MI occurred in febuxostat 80, one on allopurinol. There were 2 strokes on 80 mg and none on 40 and none on allopurinol.

[Slide]

This slide contrasts the investigator reported events versus those of the committee. It has been mentioned

that one of the things that happens with adjudication committees is that the process of evaluating the events becomes more precise because of the expertise of the evaluators, plus the fact that there are a priori definitions of cardiovascular events, which is true, and oftentimes one sees a reduction in the number of events compared to those reported by site investigators.

That actually did not occur in the CONFIRM study. The number of events were, in fact, not lowered substantially by the adjudication committee relative to what was reported by investigators. In fact, for the febuxostat-treated patients the number of events reported by investigators was one, by the committee were three. And, that is because we actually upgraded, if you will, the diagnosis of stroke in two individuals which were reported as transient ischemic attack and as a cerebral aneurysm that ruptured which actually led to a subarachnoid hemorrhage in another case. The allopurinol data were similar, as you can see, actually identical.

[Slide]

Now, these are the other kinds of cardiovascular events that did not fit into the APTC criteria. These were the non-APTC events. In the 40 mg febuxostat arm there were

10, 1.3 percent, and 80, 1.19 percent, in allopurinol 7 or 0.93 percent. There were a few more atrial arrhythmias occurring in febuxostat-treated patients in the study compared to allopurinol. About half were not hospitalized and half were based on the judgment of the clinical investigator. The other events were scattered about and didn't have any particular clustering, if you will, in one particular treatment group.

[Slide]

We then evaluated all the APTC events in the three clinical trials and examined now doses of 40, 80, 120 and 240, in contrast to a small number of patients on placebo and the allopurinol pooled data. There were, again, no APTC events on 40 nor on placebo. In the 80 mg treatment arm there were 7 for 0.55 percent; 120, 3 for 0.55 percent; 120, 3 for 0.58 percent and none on 240; and 4 or 0.31 percent for allopurinol. So, low event rates, overlapping confidence intervals, no particular category which stands out for the different kinds of APTC events.

[Slide]

In the reporting of investigator versus adjudicated for the whole Phase 3 randomized-controlled program, again, investigators reported 10, the committee

adjudicated 10, not exactly the same but similar. We downgraded one nonfatal MI because the patient had a revascularization without evidence of an MI. We upgraded one stroke that was reported as a transient ischemic attack. For the allopurinol treated patients it was 4 and 4 and had identical adjudication to the investigator.

[Slide]

These are the non-APTC events for all patients in randomized-controlled trials looking at all doses that were studied and placebo and allopurinol. Again, we have 10 non-APTC events in 40 for 1.3 percent; 15, 1.17; 8, 1.54; 1, 0.75 in 240 and 12 in the allopurinol-treated patients for 0.94 percent. Now we see that there are arrhythmias of the atrial variety. There was one ventricular ectopy case or trigeminy. There was nothing like ventricular tachycardia or ventricular fibrillation. These occurred in similarly low rates across the various treatment arms.

[Slide]

This particular figure is sort of a gestalt figure of all of the adjudicated APTC and non-APTC events in the entire febuxostat database, Phase 2, Phase 3 clinical trials and the long-term extension which originally involved about 1,200 patients that went for 3-5 years, depending on the

study, for evaluation.

Here there were a total of 134 cardiovascular events that were adjudicated in this particular assessment process. I will point out that after one year the number of patients on allopurinol dropped precipitously as most of these patients were not continuing in the extension because the investigators, blinded, chose to switch patients to febuxostat because of its better urate-lowering properties.

Febuxostat is in red and allopurinol is in green. In the first year there are fairly stable rates between the two treatments. Here is febuxostat and here is allopurinol. As we look across time, certainly for the first three years where we have a reasonably high number of patients and patient-years of observation, on febuxostat we see that the event rate per 100 patient-year is fairly similar, about 2 to 2.5 or 3 per 100 patient-year. Allopurinol shows very similar rates as well.

[Slide]

Now, I chose to go back to that original slide on the health professionals study and the MRFIT study and contrast our rates of MI and CV deaths in 4,007 person-years of assessment on febuxostat, and compare these gout patients

to the gout patients in the health professionals study, remembering that these were healthier individuals who had no prior history of an MI or stroke and the MRFIT population which meant the top 15 percent of the Framingham scoring system for increased cardiovascular risk.

So, the nonfatal MI rate in the febuxostat database was 0.40; in the health professionals study it was 0.46 and in the MRFIT study it was 0.43. Cardiovascular deaths, 0.25 versus 0.40 and 1.03. All-cause deaths, 0.40, 1.46, 2.09.

So, it looks like the event rate is relatively similar to what has been reported in the past in patients with gout. So, we think that we have a representative population in the febuxostat database.

[Slide]

In conclusion, non-clinical data did not demonstrate any mechanisms for cardiovascular toxicity. Clinical data showed no alterations in the major cardiovascular risk factors such as systolic blood pressure, cholesterol, blood sugar, body weight.

Subjects in the clinical program did have a high risk for cardiovascular events, and that is reflective of a population with gout, as we have now learned. The CONFIRM

study did not show any increase in cardiovascular event rates compared to allopurinol. There were also no dose-related increases in cardiovascular event rates in the combined randomized-controlled studies in which doses were given up to 120 in a large number of subjects. There was no increase in cardiovascular event rates over time with long-term treatment. Thank you.

Risk/Benefit and Conclusion

[Slide]

DR. JOSEPH-RIDGE: Thank you, Dr. White.

[Slide]

With regards to renal, the adverse events for renal are in the briefing document but I wanted to present the objective way of looking at renal events based on serum creatinine. We evaluated this by greater than 30 percent increase from baseline and those who had greater than the upper limit of normal. What we see is that there are similar rates across the treatment groups, with actually a low level of percentage of subjects who achieved that and actually the highest rate being seen in the placebo group.

[Slide]

When we turn our attention to the long-term extension studies using similar criteria, we see that the

rates for the total febuxostat and given by patient-year of exposure versus allopurinol are the same.

[Slide]

An important parameter to look at are adverse events by renal function. Because the CONFIRMS trial had renal subjects prospectively enrolled, we looked at that trial first and what we note is that overall the incidence of adverse events was similar regardless of renal function. We did see a small increase in renal adverse events in those subjects with moderate renal impairment but when we look across treatment groups those were similar. When we looked at the Phase 3 randomized, controlled trials the same pattern that we saw for CONFIRMS was noted.

[Slide]

With regards to hepatic, we evaluated the hepatic laboratory analyses here, in this presentation, with ALT, AST, ALT or AST concurrently, total bilirubin or the combination of ALT or AST greater than 3 times the upper limit of normal with concurrent bilirubin of greater than 2 or equal to 2 times the upper limit of normal.

What you will note is that for the febuxostat group and the low level of ALT transaminase elevations there is an increase in higher level compared to the allopurinol

dose groups. When we looked at those patients in this category we saw that these were the majority single point elevations. The majority of these subjects continued in the trial. When we look at the other lab parameters and also the other transaminases and concurrency, we see that they are parallel or similar to allopurinol.

A highlight of importance is combination, given below, where we see 240 mg had one subject and allopurinol had another subject meeting this criteria. I will discuss this in an upcoming slide.

[Slide]

With regards to hepatic laboratory analyses for the long-term extension studies, we see that the rates are fairly similar across the allopurinol and the total febuxostat group for the different levels of transaminase levels and total bilirubin. Again, the highlighted area are those with the combination of transaminase and total bilirubin. We see 2 subjects on the 80 mg dose.

[Slide]

These are the summaries of these subjects. The first 2 were in the randomized-controlled trial, the first one being on 240 mg of febuxostat, the second on allopurinol 300. We note that both of these patients had cholelithiasis

and underwent cholecystectomy and continued in the clinical study without any difficulty.

The third subject was a subject on febuxostat 80 mg in the long-term extension study who was noted to have bile duct stone and had transient elevation of her transaminases, and those started to decrease while on study drug. There were the serious adverse events reported with this subject and they are doing well.

The final subject had a fatal bile duct carcinoma. So, all of these cases were due to biliary disorders or obstruction.

[Slide]

Hypersensitivity reactionsB-Dr. Becker discussed allopurinol hypersensitivity reactions which can be severe and potentially fatal, although rare. We had one case of serious rash in the clinical program in a subject on allopurinol. This subject had an exfoliative rash with desquamation of the skin of the palms of hands and the soles of feet with loss of pigmentation, requiring treatment with high doses of corticosteroids. In this clinical program we did not see a serious rash or hypersensitivity reaction associated with febuxostat.

[Slide]

With regards to additional safety information, we evaluated other systems and events.

[Slide]

We noted that no potential risks associated with febuxostat were identified. For other clinically important laboratory evaluations we did not see any of those that were important or clinically important.

What we did note with regards to renal function is that we saw that maintenance of serum urate level over a longer period of time was associated with stabilization of creatinine clearance over that period.

[Slide]

So, in summary, our subjects are reflective of a gout population with comorbid conditions. There are no changes in nature of adverse events or increase in frequency over time. Overall the adverse events were similar across treatment groups regardless of renal function. The hepatic effects were similar to those of allopurinol, and we note in this database one serious skin reaction associated with allopurinol.

[Slide]

As I mentioned in the introduction, during the second cycle review Takeda committed to conducting a Phase 4

clinical outcome study. I will present a brief description of this study as this is the proposed study design.

[Slide]

This study will be a Phase 4 randomized, multi-center study comparing the efficacy and safety of febuxostat to allopurinol in the prevention of gout flares in those subjects with gout.

Due to the data that we have from our one-year trial and long-term extension study, we realize that this has to be a large trial, possibly 3,000 to 5,000 patients, to show a difference between treatment, and a duration, obviously, greater than one year, approximately two to three years would be needed.

We would look at febuxostat and allopurinol treatment groups. In addition to the impact on gout flares, all aspects of safety will be evaluated in this trial in order to refine a label. This study design still has to be developed with the FDA.

[Slide]

You have heard today from our presenters that gout is a progressive disease associated with multiple comorbid conditions. We see that there is a need for a new therapeutic agent. There are limitations with the current

agent, allopurinol. There are no prior adequate, well-controlled studies. Dose adjustments are recommended for patients with renal impairment. There is limited use of maximum dose resulting in the inability to achieve the target level of serum urate of less than 6, and a rare, potentially fatal or severe hypersensitivity reaction has been described.

[Slide]

We evaluated the potential risk of febuxostat. With regards to cardiovascular risk, subjects in the clinical trial had significant comorbidities, reflective of the gout population. The apparent imbalance in the small number of the cardiovascular events seen in the original Phase 3 studies was not substantiated in the CONFIRMS trial.

The CONFIRMS trial showed no APTC events on febuxostat 40 mg, and the APTC events were low and similar for febuxostat 80 mg and allopurinol. There is no underlying mechanism for the cardiovascular adverse events and we saw no changes in blood pressure, glucose, lipids or weight.

[Slide]

With regards to hepatic effects, the percentage of transaminase elevation levels were low and similar between

febuxostat and allopurinol. No dose response was noted with febuxostat. No subject met Hy's law.

With regards to treatment initiated glares, those are predictable consequences of urate-lowering therapy. More potent agents are associated with more paradoxical gout flares. Therefore, we are recommending prophylaxis with either colchicine or an NSAID in order to prevent or reduce the treatment initiated gout flares so that patients may continue on their drug for a longer period of time, so they can have the benefit of serum urate-lowering therapy.

[Slide]

You have also heard that gout is a progressive disease marked with acute inflammatory arthritis and destructive tophi. Forty mg and 80 mg of febuxostat demonstrate effective reduction and maintenance of serum urate to a level of less than 6 mg/dL, resulting in reduction of gout flares and resolution of tophi. We note that febuxostat 80 mg was superior to 40 mg of febuxostat and also allopurinol. This was effective in subjects with more severe disease, as defined by higher baseline serum urate levels or those patients who have tophi.

[Slide]

Both 40 mg and 80 mg were effective in renally

impaired subjects, and no dose adjustment was required. Febuxostat is an effective and a well-tolerated treatment option for those patients with comorbid conditions. We saw no significant drug-drug interactions with those drugs commonly used in our patient population.

Approval of 40 mg and 80 mg will allow individualized dosing options for physicians. The benefits of febuxostat clearly outweigh the risks and support the approval of febuxostat.

[Slide]

In conclusion, I will close with our proposed indication. That is, for the treatment of hyperuricemia in patients with gout the dose of 40 mg or 80 mg given once a day, 80 mg being recommended for those patients with higher serum uric acid levels and those patients with tophi.

[Slide]

A list of our consultants is presented in this slide. They will assist us in answering any of your questions. I thank you for your attention.

Questions from the Committee to the Sponsor

DR. O'NEIL: Thank you. The committee will now entertain questions, and I remind you to await recognition so that we can proceed in an orderly fashion. Dr. Glasser?

DR. GLASSER: Gosh, I have so many questions I am not sure where to begin but I will try. As a non-rheumatologist, I know this is really to focus on the cardiovascular safety issues but in order to determine risk/benefit I am trying to get a wrap around the unmet needs. I understand the renal disease issue but I can adjust doses for that. That doesn't really bother me too much.

You have shown that 40 mg of febuxostat is similar to 300 mg of allopurinol but that 300 mg of allopurinol isn't a high dose. So, I guess what I am trying to get to is this, what percent of non-responders to allopurinol will this new drug achieve your goal level? And, I didn't see data to help me with that.

DR. JOSEPH-RIDGE: our long-term data showed that, basically in our switch information we saw with long-term treatment that patients who did not respond to allopurinol actually switched and responded to febuxostat.

DR. GLASSER: Do you have a percent?

DR. JOSEPH-RIDGE: Yes.

[Slide]

So, this is in our long-term open-label extension

study where we were titrating to a level of less than 6 in serum urate after change in therapy. So, of those subjects who went from febuxostat to allopurinol, only 9 percent of those subjects were able to achieve a serum urate level of less than 6. However, if you went from allopurinol and switched to febuxostat because you weren't able to achieve that so you were not responding to allopurinol, we had 67 percent of those subjects achieving a serum urate of less than 6.

DR. GLASSER: Okay, but overall it is not a very large percentage of the total number of patients.

DR. JOSEPH-RIDGE: The total number of patients on allopurinol that switched was approximately 57 percent of subjects in the open-label study that switched.

DR. GLASSER: That is at the low allopurinol dose.

DR. JOSEPH-RIDGE: Yes, 170 subjects.

DR. GLASSER: And since this disease is primarily treated by primary care physicians, or at least predominantly, who tend to use the lower doses, you know, I am looking at the 40 mg versus the 300 mg comparison because I suspect that just as few will use the high dose of your drug versus the high dose of allopurinol.

DR. JOSEPH-RIDGE: The high dose of allopurinol is

usually not used. As you said, 95 percent maintain a serum of allopurinol at 300 mg per day, a very limited use of the higher dose. I will ask Dr. Becker if he wants to comment about the use of higher dose with febuxostat because we showed the safety profile is fine. You can use it in renally impairment patients without having to worry about dose adjustment, and 80 mg should be used in those patients that otherwise could not tolerate or not respond to allopurinol.

DR. BECKER: Thank you, Dr. Joseph-Ridge. Can we have the slide up, please?

[Slide]

With regard to the use of allopurinol, this comes from the database and the study referred to here. The distribution of allopurinol doses employed in this large database of several million people indicates that, again, 95 percent of patients receiving allopurinol were at doses less than 300 mg or 300 mg.

I think a few rheumatologists are using higher doses. I think also that, as Perez Luis has demonstrated, on average his patients, to acquire a serum urate less than 6 mg/dL, will require an average dose of about 420 mg to 450 mg per day. I don't have a lot of optimism about being able

to see allopurinol used, even with the most intensive efforts, over the course of a number of years.

Many of us have made some efforts to change the ways of our colleagues and it is not uncommon for us to recommend increases in allopurinol for patients who have not done well and, in fact, to even feel comfortable with our colleagues in the same medical center only to have them say what, are you crazy? And, then take away the allopurinol dose adjustment that we have made. There is a variety of reasons, and I think the injunction to lower the dosing in renal insufficiency is really well ingrained.

DR. O'NEIL: We actually have about three-quarters of the people on the committee who have raised their hands with questions. So, I think what we will just do is proceed around the room and then we can come back for further questions. Dr. Gibofsky, you will be next.

DR. GIBOFSKY: You have shown nice data on individuals who were not well controlled in their serum uric acid on allopurinol. Do you have any specific data on individuals who had allopurinol hypersensitivity and were put on febuxostat?

DR. JOSEPH-RIDGE: Yes, we do. We have approximately 6 subjects who had allopurinol intolerance,

who entered into the dose-ranging study that did not have an allopurinol arm. Of those subjects, 3 had GI intolerance and 3 had rash. Those subjects went out to 4 years and tolerated without significant adverse events. A small data set, but that is what we have.

DR. O'NEIL: Dr. Cush?

DR. CUSH: I have a few questions but I will ask two. You have, I would assume, no experience with the combined use of febuxostat and allopurinol?

DR. JOSEPH-RIDGE: No, we do not.

DR. CUSH: Okay. Could you explain to me why in your open-label studies you had an increased rate in gout flares at the outset of those studies compared to when the patients ended the clinical trial? At the end of your clinical trials you had flare rates of around 10-15 percent but at the onset of the open-label they were 30 and 40 percent. Would you explain that for me?

DR. JOSEPH-RIDGE: Right. When they were randomized into the open-label studies, all subjects regardless of treatment, were changed to the dose of febuxostat 80 or another dose of treatment. So, they could have been on placebo or allopurinol. They were re-randomized or given another dose of treatment.

So, we think the change in urate, just because of the change in treatment, caused them to flare. We did prophylax again but for a short period of time, at that time only an 8-week period of time.

DR. CUSH: So, did you have flares in patients who went from febuxostat to febuxostat?

DR. JOSEPH-RIDGE: We didn't look exactly at that data set. If they remained on treatment all the way through we wouldn't expect it but I don't have that specific data set for you.

DR. O'NEIL: Dr. Neogi?

DR. NEOGI: I have two questions. One is about the discontinuation rate and loss to follow-up. I was wondering if you had information as to what time during the course of the trial those individuals dropped out. Since we don't know what their cardiovascular endpoints would have been, it would be nice to know the length of follow-up of those participants.

DR. JOSEPH-RIDGE: With discontinuations and loss of follow-ups we have called subjects. There is a 30-day period within that where we follow those subjects for adverse events or events would be called in to us. And, we have very active follow-up for all subjects who have loss of

follow-up to know what their status is.

So, as far as cardiovascular events or other events, I will ask Dr. White to comment because we certainly looked at those subjects who had insufficient information on that.

DR. WHITE: Well, I think that the event rates that I spoke of were within that window. There were patients in which we actually had active follow-up within that 30-day window of follow-up. I don't recall that we actually saw any events or heard about any events that occurred outside of that period of time, understanding your question, the discontinuation rate being probably the highest in the patients on the shortest time on the drug. That is the 240 where they got flares and the 120 in which they got flares.

DR. NEOGI: Can I ask a second question regarding the gout flares at the end of study. On the graphs that you showed it almost appeared that the allopurinol arm had similar rates of flare at the end of study despite not having serum uric acid levels less than 6 at the same proportion.

DR. JOSEPH-RIDGE: You are correct. There was a numerical difference but not statistical by the end of the

one year. We couldn't really differentiate. That is why we believe in looking at the FOCUS and the long-term studies you really have to go out longer, over a two- to three-year period, to show that diminishing gout flare. So, it is a longer treatment period of time we believe. That is why our outcome study is longer to show a separation.

DR. O'NEIL: Dr. Hennessy?

DR. HENNESSY: Thank you. I have a question about the Phase 4 study that you talked about, recognizing that it is still in the planning stages. If the primary concern is cardiovascular outcomes, I am wondering if you have considered doing a large simple trial where, instead of including efficacy endpoints, you could, for the same budget, gather a lot less data in each individual patient but use that money to increase the number of patients that you are able to follow for hard cardiovascular endpoints.

DR. JOSEPH-RIDGE: In fact, our commitment is to conduct a clinical outcomes study and we believe that in doing that, as I presented, we could look at all aspects of safety. You know, there are other things that should be looked at also. But, again, we are looking at our outcomes for a clinical outcome and gathering all the information for safety with this study. As I mentioned, we are willing to

work with our regulatory agency to make sure that we design the best trial based on their recommendations. But it is a large trial and In think it is robust enough that we can capture a lot of things there.

DR. O'NEIL: Dr. Olsen?

DR. OLSEN: Just briefly on the Phase 4 trial, I wonder if you have thought about the fact that if a new drug came out how many people would sign up to a protocol that gave them a one to one chance of getting allopurinol, and if you considered that that might be a problem for such a trial.

DR. JOSEPH-RIDGE: It was interesting because when we originally started the Phase 3 studies after Phase 2 I really didn't think we would have a lot of patients who would want to go into the study. We found quite a few patients who are willing to undergo treatment and look for opportunities to be in a trial to look at this treatment for their disease because there just hasn't been a lot in a period of time, and we were able to recruit for both of our Phase 3 studies. So, we are hopeful that we will be able to do that for the Phase 4.

DR. O'NEIL: My question involves the concomitant prophylactic treatment that was given through the different

trials, and whether individuals who got naproxen versus colchicine as their prophylaxis had a different cardiovascular outcome.

DR. JOSEPH-RIDGE: Dr. White?

DR. WHITE: Thank you. We actually did have a chance to analyze that. We will be getting the slide momentarily. Generally there was no difference actually in naproxen-treated patients versus non-naproxen-treated patients. Could I have the slide up, please?

[Slide]

In looking, first of all, at all febuxostat users on the left side and allopurinol users, you will note that about 1,500 out of about 2,600 patients were users, primarily naproxen for prophylaxis, and the event rate was 0.39 versus 0.34. In the allopurinol-treated patients, the individuals who were non-users are the ones who had events, not the ones who were users. So, a very small number but no obvious pattern for NSAIDs.

Now, of interest, individuals who took colchicine versus those who didn't take colchicine had cardiovascular events in both febuxostat-treated patients and allopurinol-treated patients although, again, very low event rates at 0.5 and 0.4 percent respectively.

DR. O'NEIL: I would recommend that you look at the data again, separating naproxen from COX-2 because they have very different profiles for cardiovascular risk. In fact, in the extended studies that I had the privilege and pleasure of hearing reviewed in this forum several months ago, naproxen was the one NSAID that had a clear protective effect compared to the COX-2s which, as we all know, do not have such an effect.

DR. WHITE: Right, thank you.

DR. JOSEPH-RIDGE: Thank you.

DR. O'NEIL: Dr. Stine?

DR. STINE: I also have concerns about the drop-off rate but I wanted to bring up a different issue. As a person who has been diagnosed as having gout, and looking at some of these pictures and what can happen, I was interested in this report. But I was struck by a number that showed up on slide CS-13. Can you put that up?

[Slide]

It is that 5 over there for febuxostat, or whatever you call it. Where did that 5 go when you did the subsequent follow-up of this detailed discussion of the cardiac endpoints? That is 5 heart attacks there?

DR. JOSEPH-RIDGE: Right.

DR. STINE: And none anywhere else? I was wondering where they went in the subsequent analysis that you showed. I couldn't find them in the other tables.

DR. WHITE: These 5 in the post randomized open-label extension period? Could I have the slide up, please?

[Slide]

These patients actually occurred anywhere from 203 days in the extension up to 3 years or so in the extension, most of them occurring with no particular relationship to the timing at which they went into the extension. The 5 individuals were adjudicated to have an acute MI and virtually all had a history of *athroscelortic cardiovascular disease when they went into the trials in the first place.

So, the overall rate was 0.22 per 100 patient-years of follow-up in the long-term extension. That is a rate which I did not consider to be in excess.

MS. ARONSON: Do you have a slide available that includes the exclusion data? Particularly in your briefing document, on page 42, you mention that patients that had clinical instability due to significant medical conditions were excluded. I am wondering about those patients that were excluded and what put them out of the study.

DR. JOSEPH-RIDGE: There were in general multiple underlying conditions that would exclude them be it unstable heart failure, or unstable active liver disease. I don't know if we have the entire profile, but these are usually screened and not entered into the trials. So, we would have screening information, but based on the clinical investigator and the medical monitor at the company we would look to make sure that, you know, subjects were in good medical condition in order to enter the trial. We have the list but it is usually not part of our data set because they are not included into the study. It could be a variety of things, from severe liver because of a lot of alcohol use to severe heart failure, those type of things.

MS. ARONSON: So, there was uniformity?

DR. JOSEPH-RIDGE: Oh, yes.

MS. ARONSON: Okay, and one other question. The FACT and the APEX trials, did any of those patients go into the CONFIRMS trial?

DR. JOSEPH-RIDGE: Yes, there were a few subjects who went from the FACT and APEX into the EXCEL, the long-term study. Then we discontinued the long-term study and subsequently some of the subjects entered into the CONFIRMS trial.

DR. CUSH: How many?

DR. JOSEPH-RIDGE: Dr. Jackson, would you have that information, please?

DR. JACKSON: Robert Jackson, Clinical Science, Takeda Laboratories, Takeda Pharmaceuticals. About 12 percent of the subjects were in our previous long-term study and enrolled into the CONFIRM study.

DR. JOSEPH-RIDGE: And they were across all the treatment arms. They were not in imbalance there.

DR. JACKSON: Patients were stratified across the treatment groups based on prior enrollment in our clinical trials so they were equally distributed across the treatment groups.

DR. CUSH: Why would you enroll someone who was in one of your previous Phase 2/Phase 3 trials in another of your Phase 3 trials?

DR. JOSEPH-RIDGE: There was a three- to almost six-month period in between that period of time and requests from investigators and subjects, but we made sure that there was a long enough washout period and that they were also stable when they were entered into the new trial.

DR. O'NEIL: For the record, let me say that my fumbling mouth could not get Ms. Aronson's name out and I

wanted to clear that up. Next question? Ms. Lindley?

MS. LINDLEY: No.

DR. O'NEIL: Dr. Clegg?

DR. CLEGG: Two quick questions. First, can you just summarize the compliance or adherence? How was it monitored?

DR. JOSEPH-RIDGE: By pill counts, very rigorous monitoring, and there was over 95 percent compliance.

DR. CLEGG: Then, I am still confused by the flares that occurred through the course of the trial. Can you just summarize again? So, if a patient changed dose they received prophylaxis for a prescribed period of time?

DR. JOSEPH-RIDGE: Yes. For those who changed dose from the randomized-controlled trial into the open-label extension, for the Phase 2 they were given prophylaxis for 4 weeks. That is the original Phase 2 protocol for prophylaxis. That was prior to 2002. Subsequent to 2002 we realized we had to make the prophylaxis longer so all the subjects who went from the Phase 3 randomized-controlled into the open-label received another 8 weeks of prophylaxis. Still, that was probably too short of a period of time.

It wasn't until later, when we looked at our data and also with the new literature from *Borstadt in 2004,

that we realized that prophylaxis really has to be for a longer period of time, and now with 6 months we see lower treatment initiated flares.

DR. O'NEIL: Dr. Harrington?

DR. HARRINGTON: I have a series of questions, most of them probably pretty quick. Where were the studies performed? What countries?

DR. JOSEPH-RIDGE: The U.S. and a few sites in Canada.

DR. HARRINGTON: So, mostly U.S.?

DR. JOSEPH-RIDGE: Yes.

DR. HARRINGTON: What was the percentage of rheumatologists as principal investigator versus primary care providers, given what we heard?

DR. JOSEPH-RIDGE: About 30 percent were rheumatologists.

DR. HARRINGTON: And the rest were primary care providers?

DR. JOSEPH-RIDGE: Yes.

DR. HARRINGTON: The age, when we looked at the tables of the demographics, looks to be in the early 50s. How many patients were in the trials, say, greater than 65, greater than 70, greater than 75, the kind of patients that

actually have coronary disease?

DR. JOSEPH-RIDGE: Dr. Jackson, would you comment on that, please? If you want to ask another question, we have to look that up?

DR. HARRINGTON: The next two are for Dr. White. Were the reviewers blinded to serum urate levels? The other question is there is an awfully large number of events that were adjudicated as non-CV events. It went from, like, 327 to 200 adjudicated as non-CV events. What were those events?

DR. WHITE: Yes, the committee was unaware of the urate values. That was not something that was focused on at all. So, let me just point out that we cast a broad net on looking at potential events so it wasn't just MedDRA terms of coronary artery disorder or cerebrovascular accidents. It was much broader such as syncope, chest pain, anythingB-dizziness. It was very, very broad.

Of the 327 potential cardiovascular events, the majority, about 270 or something like that, were not considered serious adverse events. That is, they were not hospitalized nor were they life-threatening. So, when we evaluated a lot of those we did not determine that they were cardiac in nature. They were actually things like a racing

heart or palpitations or mild elevation of blood pressure which was 2 mm higher in the randomization period than it was in the screening period. Things of that nature we saw over and over again reported by the site investigators. They were exuberant in reporting of potential CV events because they had the cardiovascular worksheet to, you know, list as a possibility.

And, it was a learning experience because I have not done that before where we actually gave a non-cardiac group--that is, a non-cardiac group of investigators--a cardiovascular worksheet to work off of and they were then, you know, focusing on this as a potential. So, we probably got gross over-reporting of potential events.

DR. HARRINGTON: But when you say the adjudicators didn't focus on urate, did they know it or did they not know it?

DR. WHITE: Well, I am trying to remember if we actually saw that. If they were hospitalized there might have been a uric acid that was drawn in the hospital, or something like that, but I can't say that it was something that we evaluated at all.

DR. JOSEPH-RIDGE: I can say that all the uric levels were blinded, the whole lab. Nothing was shown to

anyone. So, they are not available.

DR. JACKSON: Just to follow-up on your question, in our CONFIRM study about 15-20 percent of the subjects were greater than 65. I don't have a breakout of how many subjects were greater than 75. And, that was similar across all of our randomized-controlled studies.

DR. O'NEIL: Dr. Furberg next.

DR. FURBERG: To compare rates of myocardial infarction and death in population studies in randomized clinical trials I find very misleading. We all know that the trials have exclusion criteria so event rates are typically much, much lower because they exclude the high risk people. So, I am not convinced by the information in slide 27.

Secondly, I would like to underscore the deficiency in the Phase 4 commitment. The trial is not set up to answer the question about the cardiovascular safety. It is too small and doesn't have the power. So, you need a much, much larger study, as was pointed out earlier. I think in addition to that, it would be good to have an observational study added to the clinical trial to get the larger numbers.

Finally, we know from experience that all these

commitments for postmarketing studies are ignored by industry sponsors. There are about 1,200 outstanding commitments. One reason is that there is no deadline agreed upon. So, I urge you, when you make your commitment, to put in a deadline so that we can hold you to it.

DR. JOSEPH-RIDGE: In fact, this trial is our commitment for the clinical outcomes study and, obviously, we haven't had a chance to discuss it with the regulatory agency. This is really to look at clinical outcomes and all aspects of safety because this is a new compound which we believe is important. We have been developing febuxostat for over ten years and, obviously, this is our third cycle and we are committed to doing this and looking at moving the compound forward for individuals with gout. So, we still have to discuss with the regulatory agencies about the commitment that we have.

DR. FURBERG: Also, if you are going to do it you ought to do it right. You have to do the study large enough so you can answer the questions you ought to answer.

DR. JOSEPH-RIDGE: The question is for efficacy and really looking at--

DR. FURBERG: I don't care about efficacy as much as I care about safety. The issue here is that you have

potentially a cardiovascular safety issue and you are not addressing it in the postmarket study you are proposing. You are setting up an under-powered study so you are not going to settle anything.

DR. JOSEPH-RIDGE: If I could have Dr. White discuss the new study?

DR. WHITE: Well, let me just address both things a little bit. First of all, I was not making an attempt to compare the rates in the sense that one was right and one was wrong. We have very little frame of reference of cardiovascular event rates in the gout population, other than those two studies, the prospective cohort study and the randomized trial of MRFIT. That is all we have to compare with.

So, when we are coming out with a brand-new drug which has 4,000 patient-years of observation with 134 events in clinical trials and we come away with event rates which are strikingly similar to those that occurred in the clinical trial and the prospective cohort study, I find that to be rather interesting. And, it would have been far more concerning to me if the event rate that was observed in the febuxostat clinical program was five times higher than it was, let's say, in the healthy professional study or in the

MRFIT study. That is all that was. There was no other hidden agenda with regards to that.

Now, with regards to the Phase 4 commitment, I think that, you know, that is a work in progress, if I might say, and I think if there were perhaps as much as 5,000 to 10,000 patient-years of observation in that study it would be an evaluation process that is double what we have right now. So, that would probably be fairly helpful.

DR. O'NEIL: The FDA apparently has a question or comment.

DR. ROSEBRAUGH: Just a comment and a point of clarification so the committee members can keep this in mind during their discussions. Now, under FDAAA we do have a lot more authority than we used to have. So, when they are commenting about postmarketing commitments, there are two kinds that have different flavors. There is a postmarketing commitment but there is also a postmarketing requirement. Under the requirement we have a lot more authority in influencing the design of the study, and we certainly put firm timelines on the studies and there are penalties if sponsors don't make those. So, I am appreciative of your comments. Certainly, if we go down that path I would like to hear more about your thoughts on Phase 4 requirements.

DR. O'NEIL: We have two more questioners who haven't had a chance to speak. First we will ask Dr. Fletcher.

DR. FLETCHER: Thank you. One thing, in looking at the data, I think it is pretty clear that when you lower uric acid and the more you lower it, the more likely you will have this risk of acute flares and, therefore, the prophylaxis.

The difference between the initial two clinical Phase 3 studies and the third larger one was the time for prophylaxis on treatment. In the first two Phase 3 studies prophylaxis was for a relatively short proportion of the time they were treated, whereas the CONFIRM study was prophylaxed for the full time and we do see a lower rate of flares in the CONFIRM study from the data that was presented.

Because we know that when you have an acute flare it tends to be a systemic effect and we know that inflammation can be an independent risk factor for cardiovascular events, I would think it would be interesting to look at the relative rates of these cardiovascular events in those patients who had a flare and those that didn't, and what was the proportion of flares in the cardiovascular

event group--the 138, however we want to cut the various events that were described--and whether there was a difference in rates there.

DR. JOSEPH-RIDGE: Dr. White?

DR. WHITE: Yes, that is an interesting question. I think that, you know, in the cardiovascular world we have all become somewhat interested in the fact that patients with hyperuricemia and gout have a higher cardiovascular risk burden. There has been some recent data showing that when you lower uric acid in hypertensive children with allopurinol you lower blood pressure. There may be some relationship between urate levels and vascular reactivity.

Now, in the APEX and FACT studies actually the rate of having an event in patients who had a flare was 0.67 percent versus those who didn't have a flare, 0.47 percent, which wasn't different. In the CONFIRM study we have 0.21 percent versus 0.19 percent. So, we didn't see an obvious discrepancy in the event rates for those patients who had a flare versus those who didn't have a flare.

DR. O'NEIL: Dr. Packer?

DR. PACKER: Just a few quick questions. You said that there was no evidence that xanthine oxidase inhibition causes an increase in adverse cardiovascular events. If

there were such evidence, would you be more worried about your cardiovascular signal?

DR. JOSEPH-RIDGE: You know, if there were precedent beforehand and there were definite models and information out there, then I would wonder whether or not this was truly an effect of xanthine oxidase inhibitor.

DR. PACKER: The reason I ask that is I just want to put into the record the results of a study called OPT-CHF, just recently published. It is a multi-center trial. And, In just want to give you the background of the concept.

Very frequently when you look at cardiovascular safety you try to look at high risk patients, patients with lots of cardiovascular risk factors or cardiovascular disease. It has become very commonplace in cardiology to look at heart failure as a high event patient population. So, very frequently if you want to know if there is a cardiovascular signal you go to the patients not only with heart disease but those with severe heart disease.

This is a trial, published several months ago, where patients with heart failure were randomized to the alloxanthine oxidase inhibitor oxypurinol versus placebo. There were 400 patients, 1:1 randomization. The duration of therapy, if I remember correctly, was 6 months and, by

intention to treat there were 31 cardiovascular deaths and heart failure hospitalizations in the oxypurinol group and 18 in the placebo group. That is an 80 percent increase in risk of cardiovascular death and heart failure hospitalization on oxypurinol, with confidence intervals from 1.0 to 3.1. The p value is 0.0546.

And, this is basically what we have in terms of randomized trials. I think we would think of this as being an important signal that xanthine oxidase inhibition in people with serious cardiovascular disease can increase the risk of cardiovascular events. I am wondering whether that changes your view of your own cardiovascular profile.

DR. JOSEPH-RIDGE: Dr. White, do you care to comment?

DR. WHITE: Well, I have to admit, Dr. Packer, I was not familiar with the oxypurinol study so it is an interesting thing that I guess we all need to look at and examine the parameters of and also the results in that population.

In the database for febuxostat there is a very small number of people with heart failure who entered in the study. It is just a handful. The only thing else I can mention is that development of heart failure in the trial

was about 0.2 percent on febuxostat and about 0.19 percent on allopurinol. So, as far as inducing the exacerbation of heart failure, we just didn't see that.

DR. PACKER: I don't think the issue is whether the endpoint should be heart failure. It is just that heart failure is the canary in the coal mine when it comes to looking for cardiovascular signals. It is so much easier to pick up a signal in a heart failure population than it is in almost any other population at cardiovascular risk.

Just two more very brief questions. Billy, you showed a comparison of risk factors of febuxostat and allopurinol but not febuxostat versus placebo. Were there comparisons versus placebo?

DR. WHITE: Well, unfortunately, there were only 134 patients on placebo, very short term, so we didn't have a big analysis done of that population. There was one event of a non-APTC variety in placebo-treated patients and no APTC events at all. So, the analysis was just not worthwhile.

DR. PACKER: Just to make sure, you said that CONFIRMS was non-confirmatory. But, although CONFIRMS was bigger, the total number of events in CONFIRMS, one, was small and, two, in fact wasn't all that bigger than the

total database that existed before CONFIRMS. So, it is not as if one could say that what you see in CONFIRMS doesn't confirm. There are just too few events in CONFIRMS.

DR. WHITE: Right. There were 2,269 patients in CONFIRMS and about 10,700 in the two other clinical trials together that were done in 2003, 2004, 2005. Event numbers were actually fairly similar for the two databases in the number of APTC events and the number of non-APTC events in total. You are right.

DR. O'NEIL: I would like to thank everyone for their discussion. We will have an opportunity to question the sponsors later during our discussion session so hang onto those questions that you have burning in your souls right now.

We will now break for lunch. We will reconvene again in this room one hour from now, at 1:20. Please take any personal belongings you may want with you at this time. The ballroom will be secured by FDA staff during the lunch break and you will not be allowed back into the room until we reconvene.

Panel members, please remember that there should be no discussion of the meeting during lunch among yourselves or any members of the audience. Lunch is

available in the restaurant of the hotel, on the first floor. There is a buffet that panel members can access.

[Whereupon, at 12:20 p.m., the proceedings were recessed for lunch, to reconvene at 1:20 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. O'NEIL: Good afternoon. This morning we heard from the sponsor of febuxostat and they have requested a moment to reply to the question regarding oxypurinol as an inhibitor of the same enzyme.

DR. WHITE: Thank you, doctor. I think we wanted to clarify this consideration that xanthine oxidase inhibition might, in fact, have a cardiovascular signal. There are three pieces of information I will very briefly mention.

First of all, that this year's American College of Rheumatology a retrospective case control study from the CHIPS database at the VA, in fact, demonstrated a significant, 20 percent, reduction in all-cause mortality in allopurinol users compared to a matched population in the Veterans system.

Second, the impact of oxypurinol in patients with symptomatic heart failure, the article that Milton Packer just mentioned by Hare et al., published in JACC earlier this year, in fact had a composite clinical endpoint that had several factors in it, and the clinical endpoint, in fact, which was the primary ITT endpoint, did not change on oxypurinol 600 mg a day versus placebo.

Finally, there are, as I mentioned, many animal models that have occurred over the course of the last several years with the development of febuxostat. Slide up.

[Slide]

This one particular study has a heart failure model of systolic overload. Once the systolic overload is developed and heart failure starts the animals are treated with vehicle, in this case *febuxostat in green and allopurinol in blue and, as you can see, the febuxostat-treated animals, in fact, had the same mortality as did the vehicle and allopurinol animals and at the time actually had a decrease in mortality.

I just want to point out that certainly the jury is still out on this and we have really very little evidence that xanthine oxidase inhibition with febuxostat induced cardiovascular toxicity or harm. Thank you.

DR. O'NEIL: Thank you. Now we move on to the presentation from the FDA. The first presentation will be from Dr. Jane Gilbert, from the Division of Anesthesia, Analgesia and Rheumatology Products. Dr. Gilbert?

FDA Presentation

Febuxostat (Uloric) for Hyperuricemia in Gout

DR. GILBERT: Good afternoon.

[Slide]

In am Jane Gilbert, as you have already heard, and I am a medical officer at the FDA. I work in the division which reviews rheumatology products and I am the clinical reviewer for febuxostat, the drug under consideration today.

[Slide]

Let's begin with an overview of my presentation. We have already heard some wonderful presentations on gout so I am only going to highlight a few points that are especially relevant for the review process that we are engaged in today.

I am then going to move on to the regulatory history. As you already know, this is the third of three submissions for this drug and what I want to do is walk you along the path that this drug has taken through the agency.

I will then move on to the second cycle, which was the cycle before the current one, and I will summarize the safety concerns that were identified at that time and which led to the approvable letter that was eventually issued. I will explain all of that in a bit more detail.

I will subsequently move on to the new trial and review for you the data there, and especially compare the

results with those that we saw in the second cycle. I am only going to briefly touch on efficacy because, as you have already heard, we really have no differences with sponsor in terms of their claims for efficacy. I will, rather, focus on safety and especially on cardiovascular safety.

[Slide]

Gout. I just want to highlight the fact that it is a common disorder, as you have already heard about, and what that means for us at FDA and those involved in the drug review process is that any new drug that is approved will actually have quite a broad audience.

We should also be aware of the fact, as I think we all are, that there are treatments available for gout, both for acute gout and for chronic gout, and allopurinol is probably the most commonly prescribed medication for this disorder.

[Slide]

Since we are especially concerned with cardiovascular safety, I want to again underline the fact that there are significant comorbidities associated with gout, and it has been estimated in a number of places that the risk of coronary artery disease exceeds 1.5.

[Slide]

Febuxostat, as you know, is being proposed as treatment for chronic gout and, like allopurinol, febuxostat inhibits the activity of xanthine oxidase and, in so doing, decreases the production of uric acid.

[Slide]

The regulatory history is a somewhat complex one. As I said before, we are now in the third of three cycles. The first cycle began when the NDA was submitted in December of 2004. At that time FDA review confirmed the efficacy of the 80 mg dose of febuxostat. At the same time though FDA review noted febuxostat's potential to result in cardiovascular adverse events.

Due to this concern about the safety profile an approvable letter was issued. An approvable letter, for those of you who don't know, is a form of communication that FDA used to indicate to the sponsor that an application was in principle approvable, though certain issues would need to be resolved. In this case it was the cardiovascular safety issue which needed further resolution and FDA requested that sponsor provide additional information either in the form of new data or re-analysis of existing data.

The second cycle began in February of 2006 with a complete response from sponsor. The sponsor chose at this

time to re-analyze existing data. However, there were two new types of analyses that were introduced. First, certain uniform categories were established to analyze cardiovascular events and, second, a formal adjudication by Dr. White was also a new part of this cycle.

Despite the new analyses that were performed, FDA review remained concerned about a potential cardiovascular safety signal and, therefore, a second approvable letter was issued. In this approvable letter FDA requested that sponsor provide yet additional data to clarify the cardiovascular safety signal with the 80 mg dose of febuxostat and/or to assess the safety and efficacy of a lower dose of febuxostat.

The third cycle began with the current submission in July of this year.

[Slide]

Let's turn now to the second cycle review. As I said, I am going to walk you through the path in the agency and share with you the findings that were of concern to FDA reviewers at that time.

[Slide]

These are the five studies that were available for review at the time of the second cycle. You have already

heard about them. There were a couple of randomized-controlled trials, as well as open-label long-term extension studies.

[Slide]

In order to assess the cardiovascular safety several categories of events were analyzed: all-cause mortality, cardiovascular mortality, investigator-reported cardiovascular events, and adjudicated cardiovascular events. FDA review of data in each of these categories concluded that there was a cardiovascular safety signal.

[Slide]

So, let's review each of these categories of events in turn. First let's deal with mortality.

[Slide]

This table displays the data for mortality in randomized-controlled trials and long-term extension studies at the time of the second cycle. As you can see, there were 12 deaths in total in the drug development program and all 12 of those deaths were in febuxostat-treated patients. There were no deaths in allopurinol-treated patients.

This raised a concern about the safety profile of the drug. However, it was also noted at the time that the mortality rate which one observes here in the randomized-

controlled studies did not go up in the long-term extension studies.

[Slide]

To get a better handle on the underlying cause of mortality, the next category of events that was explored was cardiovascular mortality. This table summarizes data for all randomized-controlled trials and long-term extension studies that were available at the time of the second cycle. What you can see here is that 9 of the 12 deaths were attributed to cardiovascular causes. Clearly, since no patients died at all taking allopurinol, there were no cardiovascular deaths cited.

[Slide]

Let's broaden the analysis a little bit and not look just at mortality but look at adverse events. Specifically, I am going to focus on cardiovascular adverse events.

[Slide]

The sponsor summarized cardiovascular events using two broad categorization schemes, investigator-reported APTC events and adjudicated APTC events.

[Slide]

I know you have already heard some about this, but

just to clarify for those of you who are unaware, the APTC was a collaborative group that devised classification criteria to perform a meta-analysis involving a large number of trials of antiplatelet therapy. The purpose of their meta-analysis was to analyze cardiovascular thromboembolic events. In order to do this with some uniformity they defined common outcome measures and those common outcome measures are nonfatal MI, nonfatal stroke and vascular death.

The relevance of all of this now is that sponsor has defined categories which are closely related to the APTC categories and also, as you well know, uses that name in the label.

[Slide]

Let's deal first with what are the investigator-reported APTC events. This table here describes the investigator-reported APTC events to you. You can see that there are two subcategories. There are primary events and secondary events. The primary events are the ones that include cardiovascular death, nonfatal MI, and so on. Secondary APTC events are those that include angina, revascularization, TIA, etc.

[Slide]

The adjudicated APTC events-we are talking here about the second cycle-are the events that were adjudicated of necessity in a post hoc fashion by Dr. White. He reviewed all deaths, serious adverse events and any events with a cardiovascular or cerebrovascular diagnosis. He reviewed data from all Phase 3 controlled trials and long-term extension studies and, of course, he reviewed these blinded to both treatment group and type of study.

[Slide]

In total, 113 events were adjudicated and they were sorted into categories of cardiovascular death, nonfatal MI and nonfatal stroke, which are the APTC categories that you have already heard about.

[Slide]

Let's turn to the data now. Let's look at the investigator-reported APTC events.

[Slide]

This table gives you the data for the APTC events in the second cycle in the randomized-controlled trials. Despite the small numbers involved, you can see that there is a numerical imbalance and a higher number and percent of individuals in febuxostat-treated arms than in allopurinol-treated arms experiencing this category of events.

Though the numerical imbalance is clear, 0.8 over 0.2 is 4, we have to ask how confident can we be that this is real and not just the result of chance.

[Slide]

In order to get a better handle on that question we have calculated a risk ratio and a 90 percent confidence interval. The risk ratio was simply that 0.8 over 0.2 or 4. The 95 percent confidence interval for that risk ratio is 0.5 to 32.

As you can see looking at that interval, it is quite broad. It includes the null value 1 as well as values less than 1, which would correspond to a more favorable outcome with febuxostat. It also includes values greater than 1, which correspond to a less favorable outcome with febuxostat. The nature of the confidence interval is such that it is not possible to determine either the direction or the magnitude of risk with a great amount of confidence.

[Slide]

This table displays the results for the same category of events, the investigator-reported primary APTC events, in the long-term extension studies. The same pattern emerges. There is a numerical imbalance with a higher rate of events in febuxostat- than in allopurinol-

treated patients. I do though want to call your attention to a fact noted by Dr. Joseph-Ridge, which is that there is extremely limited exposure of patients to allopurinol in the long-term extension studies.

[Slide]

Let's turn now to the adjudicated APTC events.

[Slide]

The picture here is not too much different from what we saw with the investigator-reported categories. There ought to be a significant overlap between the two. One thing you do note is that there is no dose response here but you do see the same numerical imbalance based on small numbers that you saw in the investigator-reported category.

[Slide]

Again we calculated a risk ratio and a 95 percent confidence interval. As before, the risk ratio is 4. The 95 percent confidence interval is 0.4 to 36. Again, it is broad, suggesting that there are limitations to how confident we can actually be about the direction or the magnitude of the risk.

[Slide]

This table simply completes the picture by providing the data for the adjudicated APTC events in the

long-term extension studies. I think I don't need to point out that the same numerical imbalance exists here as it has in the previous set of slides that we have examined.

[Slide]

So, how can we summarize the second cycle review that was undertaken at FDA? Very simply, various analyses identified a higher rate of events with febuxostat in the following categories, all-cause mortality, cardiovascular mortality, investigator-reported APTC events and adjudicated APTC events.

These data suggest a possible cardiovascular safety signal. However, as I have tried to show you along the way, there are limitations in the data that raise uncertainty about this conclusion.

[Slide]

First of all, there were very small numbers of events. Second, exposure to allopurinol was limited in the long-term extension studies. In addition, no consistent dose response was observed.

[Slide]

Finally, in the calculation of relative risk the confidence intervals are broad. They include the number 1 and make it difficult to determine the direction and

magnitude of risk with a lot of confidence.

[Slide]

Based upon the higher rate of cardiovascular events observed in the febuxostat-treated patients compared to allopurinol-treated patients, FDA felt that it could not rule out a clinically important increase in cardiovascular thromboembolic adverse events in patients exposed to febuxostat compared to allopurinol or placebo.

Because of this, FDA issued an approvable letter requiring additional data, either to clarify the cardiovascular risks of the proposed doses and/or to assess the safety and efficacy of lower doses. The purpose, of course, was to try to identify a dose or doses with a favorable risk/benefit profile.

[Slide]

So, all that brings us really to where we are today, the third cycle and the current submission.

[Slide]

However, before the current study was undertaken there were various communications between the sponsor and FDA. In preparation for a new trial, the applicant submitted a draft protocol to assess the safety of 40 mg and 80 mg doses of febuxostat compared to allopurinol.

The agency agreed with the definition of APTC events, the proposed adjudication process, and the size and associated power of the proposed trial to analyze febuxostat 40 mg.

[Slide]

The agency further indicated that interpretation of the safety of the 40 mg and 80 febuxostat doses would be difficult if a new study does not show a safety signal with the higher dose.

However, if an adequate number of events were observed in the allopurinol arm and a similar or lower rate was seen in the febuxostat 40 mg and 80 mg arms, that would be potentially informative and reassuring.

[Slide]

So, the new study was designed, undertaken, and is now completed. This is study F-153, or CONFIRMS. You have already heard about it. It is a large trial. Over 2,200 subjects were randomized in equal numbers to febuxostat 40 mg febuxostat 80 mg and allopurinol. The primary endpoint was serum uric acid less than 6 at 6 months. Allopurinol was the active comparator. Subjects were also stratified by baseline renal function in the randomization.

[Slide]

The 40 mg dose of febuxostat had not been a major focus of previous trials. It became a major focus of this trial and a non-inferiority design was adopted to assess the efficacy of the 40 mg dose of febuxostat compared to allopurinol. Specifically, a 10 percent non-inferiority margin was adopted. The basis of this number was that earlier trials had demonstrated a response rate for allopurinol of approximately 40 percent compared to 0-1 percent for placebo. Therefore, by specifying a 10 percent non-inferiority margin one could maximize the chances of observing at least 75 percent of this benefit.

[Slide]

Additional features of F-153 were that cardiovascular safety endpoints were prespecified. A cardiovascular endpoints committee was established to adjudicate events. This cardiovascular endpoints committee, as you have already heard, was a multidisciplinary group, including two cardiologists and a neurologist. This group evaluated all deaths and cardiovascular adverse events in a blinded fashion.

[Slide]

Turning to the trial and the data themselves, the demographics and the disease activity at baseline are

virtually identical in all three arms of this new trial. Specifically, cardiovascular history was equally present in those randomized to febuxostat and those randomized to allopurinol.

[Slide]

I am not going to talk about efficacy too much but I have this slide in here simply showing that over two-thirds of patients meet the primary endpoint in the febuxostat 80 mg group in all of the different trials. Febuxostat 40 mg dose, 45 percent, meets the primary endpoint and that meets non-inferiority criteria.

[Slide]

I did want to include this slide on efficacy in the renally impaired, in part because we have a question to the advisory committee on those with possibly unmet medical needs. So, this slide demonstrates the efficacy in those with mild and moderate renal impairment. You can see that in the febuxostat 40 mg group close to 50 percent meet the primary endpoint, and in the febuxostat 80 mg arm close to 72 percent meet the primary endpoint. This compares with 42 percent in allopurinol.

[Slide]

But let's move on to safety, and specifically

let's look at the safety issues that were identified during the second cycle and see how they fare in the new trial. Recall that those four categories that we looked at previously were all-cause mortality, cardiovascular mortality, investigator-reported APTC events and adjudicated APTC events.

[Slide]

Looking first at mortalityB-

[Slide]

This table shows you the data from the new trial and also shows you the data from the new trial combined with the other randomized-controlled trials. There were 2 deaths in the febuxostat group. There were 3 in allopurinol. The relative rates were 0.13 percent and 0.40 percent. As you have already seen, when you combine all Phase 3 randomized-controlled trials we have 0.22 percent and 0.23 percent for mortality. So, we have virtually identical mortality rates for febuxostat and allopurinol.

[Slide]

Turning next to cardiovascular mortality, the bottom half of this slide shows the data for the new trial, the F-153 trial. What I have on this slide actually are the data presented by sponsor. They did not assign any

cardiovascular deaths to the febuxostat-treated group. There were 2 in the allopurinol-treated group, and this compares with the previous data where there were 3 deaths in febuxostat-treated patients and none in allopurinol.

The reason I mention that these are data from the sponsor is that there actually was one death that FDA reviewers thought might be better classified as a cardiovascular death. I haven't included it in most of the tables. I will show it to you in one place. The reason I haven't included it is because it simply doesn't matter. It doesn't change the pattern of events.

[Slide]

Let's move on to cardiovascular adverse events.

[Slide]

This table describes the data for the investigator-reported APTC events in the randomized-controlled trials. At the top of the table are the numbers that we discussed before, the 0.8 percent and the 0.2 percent. At the bottom part of the table are the events and the percentages associated with the new trial. So, there was 1 event in febuxostat in the new trial, 3 in allopurinol in the new trial, with relative percents of 0.1 and 0.4.

[Slide]

This table shows you the updated data for the long-term extension studies. As I believe Dr. Joseph-Ridge already pointed out, there were an additional 700 patient-years of exposure to febuxostat between the previous submission and the current one. The event rate for the investigator-reported APTC events, however, does not go up between 2006 and 2008. It does, however, remain numerically higher than the rate seen in allopurinol. However, again, one still has the caveat which is that there is limited exposure to allopurinol in the long-term extension studies, and that remained throughout the current submission.

[Slide]

Let's turn now to the second broad category of cardiovascular events, the adjudicated APTC events. Here we see the numbers that we discussed before. Here are the new numbers. There were 3 events in the 2 febuxostat groups and there were 3 events in allopurinol. So, the percent of persons experiencing events is 0.2 in febuxostat and 0.4 in allopurinol, a difference from what we had seen previously.

[Slide]

This just completes the picture again by giving you the updated results for the long-term extension study with the additional 700 years of patient exposure. The top

line shows you the results here. The event rate is 0.6 for allopurinol and compares with 1.0 for febuxostat 80 mg, 1.0 for 120 mg. The total is 1.0. The rate of 2.7 here is probably misleading due to the fact that there are a small number of people there, but it is there.

[Slide]

This is one of my favorite slides because what I tried to do here is put it all together. You know, between this morning's presentation and my presentation you have had a lot of numbers thrown at you, to say it very simply. So, what I tried to do was to put this altogether here, and this is an overview for the new study. The next slide will be an overview across studies.

What I have done here also is divide this between the febuxostat 40 and febuxostat 80 arms rather than lump them together as I did in the previous slides. So, you can look for each of the categories of events that I have just reviewed and you can see what the percentages are. So, for mortality, 0.1 percent of people died in febuxostat 40; 0.1 percent died in the febuxostat 80 arm; 0.4 percent died in allopurinol arm.

What you see here is that except for the single category of secondary investigator-reported APTC events in

the febuxostat 40 arm, all of the percents are lower in the febuxostat arms than they are in allopurinol.

I need to clarify this 0/1*. Basically, that is there indicating either the exclusion or the inclusion of an individual, as I mentioned before, who we think maybe should have been classified as a cardiovascular death. The point is merely to show that if this individual were included as a cardiovascular death, then 0.1 percent of individuals would have died in this arm and that compares with 0.3 percent in the allopurinol arm.

[Slide]

This slide is another one trying to put it altogether for you. What it summarizes is the relative risk across different doses and across the 3 randomized-controlled trials for a single category of events, the adjudicated APTC events.

What you can see if you look at this slide is that for the older trials, 009 and 010, the relative risks are all between 2 and 3. For the new trial the relative risk of febuxostat 40 mg compared to allopurinol is 0.1. The relative risk of febuxostat 80 mg compared to febuxostat [sic] is 1. I think it puts some of this together, I hope, for you.

There are two additional facts which can be gleaned from this table. First, we don't see any dose response so the relative risks are essentially straight-lined across the different doses of febuxostat in the older trials.

Second, if you look down here, even at the febuxostat 40 mg relative risk, and you look at the confidence interval, although it is narrower than some of these up here, the confidence interval still is broad, 0.01 to 2.76. It includes values that exceed 1 and, therefore, does not enable us to exclude a risk with febuxostat.

[Slide]

As part of our review process, we consulted the Cardiorenal Division at the FDA and asked the folks there to assess whether the overall pattern of cardiovascular events presented in the febuxostat trials suggested an increased cardiovascular risk. Our consultants did not identify a pattern suggesting a risk with febuxostat in the new study, study F-153. Our consultants also noted that applicant's analyses of combined trial data did not suggest greater rates of cardiovascular events with febuxostat compared to allopurinol. No further cardiovascular studies were recommended.

[Slide]

Sort of a footnote here is this slide on special populations, again, as it relates to the fact that we have posed a question to the committee on special populations and unmet medical needs. But I think it is important to consider populations who are likely to take febuxostat if it is to be approved.

There are a couple of populations that might be categorized as having unmet medical needs. One group would be those that are refractory to currently available treatment. A second group is possibly those with renal impairment. I just want to emphasize that we have looked at data for the renally impaired and no specific safety signal was identified in that group of individuals.

[Slide]

How can we summarize? As follows: Review of earlier data suggested a cardiovascular safety signal. However, the interpretation was complicated by uncertainty due to small numbers of events, the absence of a consistent dose response, lack of prespecified endpoints, post hoc analysis and broad confidence intervals consistent with either an increased or decreased risk compared to allopurinol.

The new study, F-153, provides additional information regarding cardiovascular safety and it has certain attributes that we should pay attention to. There were three-fold more patients in each arm than in previous studies. There were prespecified cardiovascular endpoints and an adjudication committee had been established to review events. The baseline cardiovascular risk in this trial was similar to that seen in earlier trials.

[Slide]

Additionally, throughout the development program data support the efficacy of the 80 mg dose of febuxostat based on superiority to allopurinol. In the new trial the efficacy of the 40 mg dose of febuxostat was demonstrated based on non-inferiority to allopurinol in study F-153.

Cardiovascular events in the new study were few in number, both in total and in individual arms. But for events that were seen the rate was not higher with febuxostat 40 mg or 80 mg than with allopurinol. However, statistical analysis based upon calculation of confidence intervals does not really enable one to exclude the possibility of an increased risk with febuxostat.

[Slide]

So, the issue for discussion, taking into account

the totality of the data, including the older as well as the new trial, and considering their respective strengths and limitations, the FDA is asking the committee to provide its assessment of the risk/benefit relationship of the 40 mg and 80 mg doses of febuxostat.

Questions from the Committee to the FDA

DR. O'NEIL: Thank you. At this time I would like to invite questions for the FDA from the committee. Again, I would like to remind you that speakers must be recognized by the chairman before we go forward. Dr. Gibofsky?

DR. GIBOFSKY: Dr. Gilbert, I wonder if it was known at the time the analysis was done that, as we learned earlier, approximately 12 percent of the patients in the CONFIRM study were included in the analyses from the previous trials. If that were the case, if that 12 percent population were excluded what the analysis would be.

DR. GILBERT: I believe that those patients were stratified at the initial randomization so we were aware of the fact that they were included and did not think that they influenced the results.

DR. O'NEIL: I think we will probably just go this way this time. Dr. Glasser?

DR. GLASSER: I am not questioning the efficacy of

febuxostat. But when you compare the 80 mg dose to 300 of allopurinol I don't think that is a fair comparison since you are using one drug at the lower end of the dose and the other at the highest. So, the efficacy of equivalent doses I think remains a question to me, not that the drug is not efficacious.

My concern is what is going to happen will be the same thing that has happened to almost every drug that has a dose range. The most common dose used will be the lower dose. So, I think, from the efficacy standpoint, that is a concern I have.

Could I ask one brief question to Dr. White? Well, it is to Dr. White so I will ask it later.

DR. O'NEIL: Yes, go ahead.

DR. PACKER: One question, at the end of the second cycle there was a concern about a potential cardiovascular safety signal. FDA then asked the sponsor to do another trial. The trial that was done defined certain cardiovascular procedures in a better way. There was a prospective adjudication process and there was a more prospective definition.

But if you really wanted to clarify the interpretation of small numbers of events, one would think

that the one thing you would want is larger number of events. Was there any consideration in CONFIRMS when there was a discussion about it about designing it in such a way that you would actually get more meaningful cardiovascular data, i.e., getting individuals at higher cardiovascular risk in the study; designing the study to achieve at least some sense of cardiovascular events?

The reason is because this is actually in some ways a cardiovascular safety study, but it has as little power to look at cardiovascular safety as the previous trials.

DR. GILBERT: Good question. I was not there at the time. I am going to turn it over to Dr. Siegel who, I believe, was present during those discussions.

DR. SIEGEL: At the time of the end of the second cycle there was a variety of considerations in the design of this new trial. The main concern was to see if the signal that was seen in the previous trials would be reproduced in the subsequent study.

It had not been concluded at that time that a formal cardiovascular outcome study was necessarily required. On the other hand, we did believe that it was important to have enough events, as Dr. Gilbert stated, to

be able to reach conclusions about the safety of 40 mg and 80 mg if it turned out that the percent of patients with events was the same or lower.

So, we did recommend to the company to make sure that there were enough events to be able to reach conclusions. Unfortunately, this study had quite few events so it is difficult to reach firm conclusions.

DR. PACKER: Did the original protocol have any estimates of cardiovascular events, or any sense as to when the study were done what the upper bound of the confidence interval might be based on the projected number of events?

DR. SIEGEL: I think the company may want to comment on their estimates of the number of events. They did estimate the number of events they expected to see based on the earlier studies, and the number of events that were seen was far fewer.

They also included some estimates about the power to detect different levels of elevation of risk. These were fairly crude and it wasn't designed to rule out, say, a 25 percent increase as a formal cardiovascular outcome study would be.

DR. PACKER: Right, but my sense is it wasn't designed to rule out a two-fold or three-fold increase

either.

DR. SIEGEL: It was.

DR. PACKER: It was?

DR. SIEGEL: Based on the estimate of the number of events and the size of the study, it was estimated that the study could rule out, based on the 95 percent confidence interval, an increase exceeding about 2.5 or 2.8.

DR. PACKER: I am sorry, one last question, in all of these discussions was it assumed that allopurinol was neutral for cardiovascular issues?

DR. SIEGEL: In general terms, it was. We didn't formally address the issue of whether there was a cardiovascular safety signal with allopurinol but at the time we weren't aware of any data to suggest that the rate of cardiovascular events would be higher with allopurinol. So, that was, indeed, the assumption.

DR. O'NEIL: Dr. Fletcher, do you have a question?

DR. FLETCHER: From reviewing the package from the FDA, it would appear from what you said, Dr. Gilbert, that at the beginning of the CONFIRM study they were well balanced with regard to all the cardiovascular risks, all of the factors, and so forth.

But in retrospect, in looking over the study, is

there any suggestion that the level of kind of general inflammatory response across the two groups is different? That is, it would appear that the frequency of flares, and maybe the magnitude, I can't tell, the number of flares, gouty flares that occurred in cycle two program seemed to be quite a bit higher than in cycle three. That seems to be related perhaps, or might be related to the continuous prophylaxis throughout the CONFIRM study versus the relative shorter period of prophylaxis. Is there any suggestion in the dataB-number of flares, magnitude, length of flares, in the earlier set of data that would make you think the course of treatment was different?

DR. GILBERT: If you are asking about the differences between the prior randomized-controlled trials and the current one, I did pore over the demographics in those different studies and did not find significant differences between them. So, I think that we are dealing with comparable populations both previously and now.

And, I think that the treatment differences were well explained by Dr. Joseph-Ridge. There was less prophylaxis in some of the earlier trials. In this particular trial, as I understand it, there was 6-month prophylaxis. They were prophylaxed basically throughout the

entire trial.

DR. FLETCHER: Right, but that didn't suggest that longer prophylaxis resulted in a lower frequency of flares in the CONFIRM study.

DR. GILBERT: I have not specifically analyzed that.

DR. FLETCHER: Thank you. I just wanted to know whether you had.

DR. O'NEIL: Dr. Furberg, do you have a question?

DR. FURBERG: No.

DR. O'NEIL: Dr. Harrington?

DR. HARRINGTON: Dr. Gilbert, I don't know if this will be for you or Dr. Siegel. I just want to follow-up on a couple of points that Milton has been getting at, the first of which is that we keep saying that this is, you know, a high cardiovascular risk population. In fact, risk is not driven largely by the things that were being included in the study. Most of these people are overweight, middle-aged men. We are not seeing a high number of older individuals with overt vascular disease.

So, I think we need to clarify a little bit who was actually enrolled. I wonder if there was any discussion with the sponsor at the time as to truly enrolling an older

group of patients with coronary disease, with peripheral vascular disease whereby these signals might be detected.

Likewise, I wonder how the sponsor came up in discussion with you with the six months, which is a very, very short period of time to uncover cardiovascular risk for a drug that is going to be taken, from what I heard this morning, lifelong.

DR. GILBERT: We have looked at the incidence of APTC events in subjects who had a history of prior cardiovascular disease and those who did not have a history of prior cardiovascular disease, and we did not see a relationship there. So, we did not see that those who took the medication who had prior disease developed a higher rate of events.

DR. HARRINGTON: That was an exceedingly small group of people, was it not?

DR. GILBERT: Well, I think the numbers on one of my slides were approximately 57 percent who had cardiovascular diseaseB

DR. HARRINGTON: But that included hyperlipidemia, hypertension and not overt coronary disease.

DR. GILBERT: It was any cardiovascular history.

DR. HARRINGTON: Right, it is mostly risk factors.

You know, the fact is people who are 50 years old with a bunch of risk factors, they don't die.

I mean, Milton made the point this morning of heart failure beingB-I think he called it the canary in a coal mine, and the only way you really see these effects, you know, to go back to the COX-2 story, is when you start exposing the 65-year old with multi-bed vascular disease. But we don't have those patients and I just wonder if some discussion had taken place as to why not.

DR. SIEGEL: Let me try to address that. As I mentioned before, the agency did not specifically ask the company to carry out a cardiovascular outcome study, which would have been done if we had had more certainty or more reason to believe that the cardiovascular safety signal was real. At the time we thought that it looked like there may be a signal but it wasn't certain that there was.

So, the purpose of the trial that we asked the company to do was to basically repeat the types of studies that were done before to see whether there was any signal. So, that is the reason the studies were carried out for 6 months as opposed to much longer, which is what you would want to do if you were doing a cardiovascular outcome study, and why we didn't particularly insist on having people at

higher risk.

Nonetheless, as Dr. Gilbert said, 50 percent or so of the patients did have cardiovascular risk factors and approximately 15 percent had a previous history of cardiac disease. Nonetheless, I think these are points that are well taken, and a study that had included more people at risk may have been more sensitive to detect a signal.

DR. O'NEIL: Dr. Clegg, do you have questions?

DR. CLEGG: Just a brief question for Dr. Gilbert to confirm something that I think I heard her say. The population of the 153 trial was similar to the others. I was looking to see if I could find the slide, but it seemed like the BMI, for example, was quite a bit lower in the 153 trial than it had been in the previous trials.

DR. GILBERT: I didn't pick up significant differences.

DR. CLEGG: Okay.

DR. O'NEIL: Ms. Lindley?

MS. LINDLEY: I think my concern, as I am not a clinician like the rest of you are but I am a caregiver for a person who has chronic gout and he is one of the ones that has unmet needs or is part of the unmet population, and I worry about the exclusion criteria and how that will affect

him later on if he were to receive this treatment.

DR. GLASSER: I didn't hear the last part of your comment. How it would affect him if what?

MS. LINDLEY: How do the exclusion criteria work with someone who is part of the unmet population, and will that be a factor, and will there be follow-up with that?

DR. SIEGEL: I would like to hear more about your concerns regarding the exclusion criteria. When we work with companies to develop trials we do have an opportunity to encourage them to enroll a patient population that is more like the patients who will receive the drug after it is approved.

I think it would have been impossible to enroll patients in the efficacy trials who weren't candidates for allopurinol because one of the treatment arms was allopurinol. Nonetheless, there are other ways that you can make sure that the exclusion criteria aren't too narrow. Are there particular concerns that you have that you would have liked to see addressed?

MS. LINDLEY: The renal impairment was the main one

because he is not a candidate for allopurinol.

DR. SIEGEL: Thank you.

DR. O'NEIL: Ms. Aronson, do you have questions?

MS. ARONSON: I am trying to get to study F-153 again. I notice the sponsor's slide CV-17 is across the board. About 60 percent were either on NSAIDs or aspirin but that is concomitant medications and I don't think that includes prophylaxis. Is that true? My question is that under the briefing information that we got from the sponsor, page 166, concomitant medications listed corticosteroids.

So, from my lay perspective I have a question about whether any of you or any of the physicians could answer if there was a high percentage of corticosteroids across this 6-month arm. Would that mitigate or moderate any of the cardiovascular events?

DR. GILBERT: Do you want to answer that?

DR. JACKSON: In our clinical trial the corticosteroid use was very low. The majority of people for prophylactic therapy received either naproxen, as we discussed, or colchicine. In the 153 study specifically about 80 percent of the subjects received colchicine and about 20 percent received naproxen, and less than 1 or 2 percent received corticosteroids.

DR. O'NEIL: Dr. Stine, do you have a question?

DR. STINE: I guess my question at this point is more for the FDA than it is for the manufacturer. Just thinking about Dr. Packer's presentation this morning, he showed slides where, you know, if you keep testing something and you test it again and you test it again, the results bounce around as you do this continued testing. And, I was struck by how similar the exercise that we are now engaged in is to exactly the slide that he showed. Namely, how do we decide safety? Do we keep testing? If it doesn't look safe, well, let's test it again and maybe it will look safe if we test it again. Well, let's test it again and maybe it will look safe this time.

I understand the desire and the need for more information. I certainly appreciate and applaud that exercise, but there does come to be a point where one has to resolve yes or no, and statistics never give you a definitive answer. So, at some point one has to resolve, you know, where do we stop in this process. We can't just stop whenever we get a result that we like or a result that we think is the right answer. Otherwise, whey the hell bother to do the study.

So, I don't think it is necessarily the whole

point of this exercise, but I think in general going forward the agency has to give some careful thought as to how this process ought to be managed. Thinking of it as a process doesn't necessarily have a strict one-time shot.

DR. GILBERT: I think that you have encapsulated the essence of the problem that we face today, which is sort of how much is enough, and where are we in the process, and have we reached the end, and can we have enough confidence in the data that we are looking at now or do we need more data? I think you have summarized it beautifully.

DR. O'NEIL: Dr. Furberg, do you have a point to make to this point?

DR. FURBERG: Yes, it is triggered by what you said. I mean, what Milton showed were some extreme examples, a small study showing a trend and then when they did a full-scale trial it flipped. I can tell you that for most studies it is the other way around. You see something and you do the study and you confirm.

So, I think we shouldn't be misled by his slides. They were fascinating, reminding us that we can't be certain. But his point was not that small trends always go away. That is not what he intended to say.

DR. O'NEIL: I have no questions at this time. Dr.

Olsen?

DR. OLSEN: I am just curious to know if you ever looked at uric acid itself, regardless of what drug the person was on. In other words, if you took allopurinol and you got uric acid below 6 in terms of cardiovascularB-maybe that is a very small group, but if you just, like, made uric acid a variable and looked at the cardiovascular profile, forget what drug they were on, what the results look like.

DR. GILBERT: I haven't looked at that, not within this study. There are articles out there and studies where people are looking at uric acid and its relationship to cardiovascular disease and I believe it is a study such as that which prompted the study with oxypurinol that was discussed earlier.

DR. OLSEN: It is still hypothetical I guess, but if you really got your uric acid low you should reduce your cardiovascular risk. So, if you saw an equal number of incidents in groups where they didn't get quite as low as the other group, then maybe that is actually a group doing worse than you would expect because of a drug effect that is independent of uric acid level.

DR. GILBERT: That is possible.

DR. PACKER: I think it is probably important, just