from the cardiologist's point of view. The concept of whether uric acid is an independent risk factor is still very much up in the air. Even if it were, it doesn't mean that reducing it reduces cardiovascular risk. Any analysis of events based on changes in uric acid after randomization is essentially a subgroup analysis based on a post randomization event, which is terribly hard to interpret.

So, I just want to make sure that everyone is okay. I don't think the cardiologists think that anyone has shown that reducing serum uric acid reduces cardiovascular risk.

DR. O'NEIL: Dr. Hennessy?

DR. HENNESSY: Thank you. We have heard some preliminary plans from the sponsor for Phase 4 studies that have a number of goals, one of which might be to assess cardiovascular outcomes. I mean, it seems like those plans are fluid at the moment. Has the agency given any thought, if this drug were approved, to what sorts of postmarketing requirements would be imposed, and whether they would include a randomized trial, maybe a large simple trial that would be able to rule out increased cardiovascular risk of some given magnitude?

DR. GILBERT: I don't believe that we have. As you

said, things are fluid right now and we haven't gotten around to really discussing what the postmarketing requirements would be. I believe that is a question that we have asked the committee and certainly would appreciate input from you as to what you think would be necessary and desirable.

DR. O'NEIL: Dr. Siegel?

DR. SIEGEL: That is absolutely right. We have had some discussions, of course, preliminarily but that is the purpose of this committee, to hear your views about it and, based on that, we will think about that with what we have thought so far and come up with a plan that addresses all the concerns.

I did want to address the concern that Dr. Olsen mentioned about shouldn't the cardiovascular outcomes be improved if you reduce uric acid. I think Dr. Packer made most of the main points but I want to make one other. In the New England Journal about two or three weeks ago there was an excellent review of the data on uric acid and cardiovascular outcomes.

One of the points that they made is that uric acid may have a different effect early versus late in disease. So, it may be that never having an elevated uric acid might

reduce your cardiovascular risk, but reducing it when disease is well established, you can't necessarily say that it would.

DR. O'NEIL: Dr. Neogi?

DR. NEOGI: I had a question that I am not sure that Dr. Gilbert can answer but perhaps Dr. Joseph-Ridge. Given the emerging evidence about the problems with uric acid being too low in terms of neurologic issues, was there any signal seen in the long-term extension studies with stroke recovery or other neurologic abnormalities?

DR. GILBERT: I will let Dr. Joseph-Ridge handle that.

DR. JOSEPH-RIDGE: For the long-term studies we made sure that serum urate did not go below 3. There were a few instances where they transiently went below 3 but that was one of the requirements, to keep that at the low level of normal. So, we did not allow that. So, that information on low uric acid and adverse events, we don't have that.

DR. O'NEIL: Dr. Cush?

DR. CUSH: What was the agency's request of the company as far as studies in patients with renal impairment? Is there anything else that hasn't been thus far presented?

DR. GILBERT: We did not have a specific request

with regard to renal impairment that I am aware of.

DR. SIEGEL: Could you clarify the question? What were you looking for in regard to what the agency might have asked for in renal impairment? Did you have a concern?

DR. CUSH: Well, I will get to this later. I think that what has been stated over and over today is that no one has any problem with the efficacy data here. If efficacy is lowering of serum uric acid, I think we are all in agreement.

My primary goal in treating gout is treating gout, not a number. So, are we making patients better clinically beyond their laboratory levels? And, one of the things that has been thrown around here today is that there may be a substantial need for this kind of therapy in patients who have allopurinol hypersensitivity issues, for which we really don't have any studies with this compound, and for patients who have renal impairment, for which we have a glimpse in some early data to suggest that it seems to be safe and effective in those people. But I don't know that we have hit any major benchmark as far as that goes since that wasn't a requirement of a sub-study or a large study to actually answer that question.

DR. SIEGEL: I can say that the unmet medical need

population was not a primary focus of the clinical development program. Some data were collected, of course, in potential medical need populations but that wasn't the primary focus and, if it had been the studies would have been, of course, designed differently.

What was the other issue? Oh, yes, with regard to clinical outcomes. Yes, it would be great in a clinical development program like this to document decreases in gout flares and resolution of tophi. Unfortunately, the time-frame for measuring those outcomes can be fairly lengthy. Some of the data suggest two years or even longer. It is difficult to maintain a blinded controlled trial for that long although, in principle, it might be able to be done and we would love to hear your comments about situations where that would be critical or important.

DR. O'NEIL: Well, I have come up with one quick question and I am not sure whether it is directed to the FDA or if the FDA would prefer to bump it to the sponsor. But in the line of special populations, as the sole pediatrician I think in the room, I wonder if the special population of pediatric patients is going go be addressed at some time in the future.

Furthermore, most of those have underlying renal

disease, but there are metabolic disorders as well, children that have very high uric acids that deposit in the tissues and have secondary disease related to that. Moreover, the renal failure patients, are there plans to go for an indication in renal failure perhaps?

DR. GILBERT: What I am aware of is that the company, I believe, is seeking a pediatric exclusion for this disorder. Whether or not they have plans in the future to pursue an indication in the pediatric population I don't know.

DR. JOSEPH-RIDGE: Currently we are looking at the management of gout. You are correct, that would be another population, another disease state and we would have to open discussion with the FDA regarding those populations that you brought up.

DR. SIEGEL: There are a number of different routes where the FDA can encourage or require a pharmaceutical company to do studies in children. One is PREA. Where there are an adequate number of children with the disease corresponding to the disease in adults the FDA requires companies to do studies, safety, dosing and in some cases efficacy studies as well. The other is the BPCA, Best Pharmaceutical for Children Act, where, if there is a need

there is a way of encouraging sponsors to do trials.

It is my understanding that in gout the number of children with gout has been considered very small so it is difficult to do clinical trials. Nonetheless, we would be very interested in hearing your thoughts about what the unmet medical need population is so we could work with sponsors to try to collect those data. Do you have a sense about the number of children and who you would want studied?

DR. O'NEIL: I am afraid that the number of children with clinical gout is extremely small. I have probably seen three or four cases in my career. So, that tells you it is quite small. But the pediatric nephrologists could probably give you a better handle on the number of individuals with significant hyperuricemia.

The other thing is that children with metabolic disorders do not tend to go to pediatric rheumatologists for control of their hyperuricemia but, rather, that is handled by the metabolic specialists who care for them. So, those are sort of two other groups of clinicians that we may need to contact to find out what the population might be. Dr. Glasser has one more question.

DR. GLASSER: I was wondering if the FDA and the Dr. White's committeeB-what criteria they used for MI. I

know they talked about two or three criteria, chest pain, EKG changes and enzyme levels but chest pain is variable and soft. I don't know for the EKG changes whether they used Minnesota codes or just subjective analysis. But the bigger variability recently is what upper level troponin levels or other enzymes were used, and that could certainly change the numbers of MIs. Now, you might think it would do it equally in both comparator and active group but that may or may not be so. So, could you just give us a brief overview of that?

DR. GILBERT: I can give you what I have but Dr. White is standing at the mike.

DR. WHITE: I thought you might want me to do that.

DR. GLASSER: Do you have a slide?

DR. WHITE: I don't really have to use a slide for that, but we, of course, evaluated the quality of the chest pain and made sure that it was consistent with what would be typical angina. Sometimes that is not always possible by the verbiage that is in our clinical record.

I will tell you though that in almost every instance when somebody was hospitalized for an SAE we had source documentation for the adjudication process. We did not simply have CIs or where the investigator, you know, jotted notes on a case report form.

So, that allowed us to see the electrocardiograms or full descriptions of electrocardiograms and we did use the criteria of two continuous leads that had injury currents and/or development of new Q waves. We also utilized both the MB fraction and the CPK as well as troponins and in most cases we had both, and they had to meet the outside limits of the laboratory where they were done. They were not centralized. They were done by the various hospital laboratories.

DR. GLASSER: Yes, but, Billy, the upper limits of normal are sometimes given as one value, two values and three values.

DR. WHITE: Oh, I see. Yes, for troponin that you are speaking about in particular there are intermediate levels. So, in that case we would typically be using the outside limits of troponins in most instances if that occurred. For example, the common scenario is if someone has an angioplasty their troponin bumps a little bit and it goes into the indeterminate, intermediate range we would probably not have called that an infarction.

DR. O'NEIL: One last question?

DR. PACKER: This is a question to anyone who can answer it. One of the very important principles when you

look at cardiovascular events is to follow all patients for the planned duration of the study. So, if it is a six-month study all patients are followed for six months whether they remain on drug or not.

In this case, if a patient in 153 dropped out of the study after two months were they followed for cardiovascular events for the entire planned duration or only for 30 days?

DR. JACKSON: In the clinical program we followed patients only for 30 days after the study, but that was only if patients reported an adverse event. So, we followed them for 30 days post that adverse event or to resolution of that adverse event.

DR. PACKER: I know that is the conventional practice but it just really is important for everyone to realize that that actually is not the way to capture cardiovascular events. If you want to do cardiovascular safety and retain the protection of randomization, you ought to follow all patients for the planned duration of the study even if it means four months, or whatever, and whether they remain on therapy or not.

Questions to the AAC and AAC Discussion

DR. O'NEIL: Thank you. Thank you, Dr. Gilbert.

The committee will now turn its attention to the task we have been assigned, the careful consideration of the data before this committee regarding the safety of febuxostat. The committee has been asked to address four principal questions. The first is the safety of the drug and the safety, in particular, at doses of 40 mg and 80 mg. The second is appropriate dosing. The third is its use in special populations. Then, the fourth is a vote on recommending approval of the drug for chronic gout. We have follow-up questions for that depending on the outcome of that vote.

I would like to remind the committee and all present that the two gentlemen to the far right, Dr. Fletcher and Dr. Packer, are non-voting members of the committee.

So, the first question, the safety of febuxostat: In its review of the two initial Phase 3 trials, studies 009 and 010, of febuxostat 80 mg and 120 mg, the FDA found a larger number of APTC-defined cardiovascular thromboembolic events in the febuxostat arms compared to the active control allopurinol arm. In the subsequent Phase 3 trial, F-153, of febuxostat 40 mg and 80 mg the event rate for cardiovascular thromboembolic events was not increased with either

febuxostat dose compared to the allopurinol control. However, the event rate in the control group was low.

Our first question is to please discussion the strength of evidence suggesting a cardiovascular safety signal for the febuxostat 40 mg dose.

Then secondarily, discuss the strength of evidence suggesting a cardiovascular safety signal for the febuxostat 80 mg dose. I would like to open the discussion.

Excuse me, I overlooked one very important technical detail. No one signed up for the open public hearing so we are not proceeding with that.

DR. GLASSER: Well, I will answer the easy question first. I am sort of convinced there is not a dose-response relationship so I have no problem between the two. I am still laboring with the harder part of the question.

DR. PACKER: Steve, how do you know there is no dose-response relationship?

DR. GLASSER: I don't know that there is not. In the data shown there is no evidence of that.

DR. PACKER: I would just add that the data are insufficient to know the relationship between risk and dose.

DR. O'NEIL: Dr. Furberg?

DR. FURBERG: I think the question is a little bit

too broad for me because they are asking about safety and the information we have is very limited. We have information on a low risk group where the event rate is lower than expected. We don't have good information about potential use. There are still all the people with concomitant diseases.

The other limitation is that we only have information up to, say, about six months or so. So, we don't know the long term. So, the issue is, or at least my interpretation is that in the lower risk group up to six months there may not be much evidence of harm. For the rest I have no idea because we have no data.

DR. O'NEIL: Dr. Cush?

DR. CUSH: I agree with you, Dr. Furberg, although I don't know that I would call these a low risk population because of all the comorbidities, and gout in itself is not necessarily low risk. This is sort of maybe a real-world risk because this is what patients really look like. But I do agree with what you said.

DR. O'NEIL: Dr. Harrington?

DR. HARRINGTON: Yes, I think we need to keep coming back to Curt's point that--and, again, these may be the gout patients with cardiovascular risk factors--the

patients that cardiologists are going to see with gout are not these patients. So, I think that the point that has been made is that we have an insufficient database to draw inference around the cardiovascular risk in patients who have cardiovascular disease.

DR. PACKER: Of course, one of the things that plague the discussion here is whether allopurinol is neutral. I wish we knew the answer to that question. Again, the signals that we have would indicate that there are reasons to be concerned. There are reasons to think that allopurinol could increase risk. In fact, the sponsor showed one animal study in heart failure where allopurinol did worse than the control group.

I hate animal studies in heart failure. They can be terribly misleading. But in human studies oxypurinol which, by the way, is the active metabolite of allopurinol, was associated with an increased risk in a population that we consider to be the canary in the coal mine.

So, I am nervous if we are going to find reassurance in comparing this drug with allopurinol, which may or may not have a risk and could very well have a risk. I fully appreciate the fact that we need to take into consideration that when physicians seek to lower uric acid

they have to use something, and that it could be that the drug they use every day increases cardiovascular risk.

But we have to separate the question as to whether this drug has a cardiovascular risk greater than conventional therapy or whether this drug has a cardiovascular risk, period, when compared with placebo. It could be that we would decide that it could have a cardiovascular risk compared with placebo but that the comparison here should be with allopurinol. This is actually something probably worth talking about.

DR. O'NEIL: Dr. Cush?

DR. CUSH: I agree with Dr. Packer and his concerns. Whether allopurinol is neutral or not I think is a very important question that won't be answered today, but it is still the standard against all therapies going forward that will be judged so I think there is some value in that.

One of the points that I wanted to bring up earlier this morning that some of this is related to, as Dr. Fletcher pointed out, is the flares of disease that are brought on by lowering urate, and that we saw significant flare rates that continued on for many, many, many weeks and only until you get to the very end do you get to see a real

benefit between the drugs, and that is sort of marginal but significant.

We know about CRP and who are in the upper tertile and normal CRP ranges and what that does to cardiovascular risk. Is some of this very difficult to interpret risk related to these events that, you know, by lowering uric acid we are doing a good thing but and, at the same time, we are also inducing attacks that expose a patient to minor bouts of inflammation in patients who are predisposed to these small event risks that we see with these kinds of numbers?

It becomes very difficult to then figure out. So, one of the questions I would want the sponsor to look at is maybe you can look at time or area under the curve where CRP is elevated or in the upper tertile of normal and see how that relates to some of these events, those who are within that upper level or unacceptable range and those who are in the very acceptable range, to see how much inflammation they are living under while they are on such therapy and having their uric acid lowered.

I know we are straying from the question at hand because I don't think anybody has a problem with 40 mg versus 80 mg and the whole dose issue. I think we are still

going to grapple with are we going to see in the end that there is no cardiovascular risk? Can we be certain of that? That is going to be the hard question.

DR. O'NEIL: Dr. Cush, did you want a response from the sponsor on whether they have data on inflammatory markers?

DR. CUSH: Yes, have you done an analysis that looks at, again, the relatedness of CRP elevations to some of these cardiac events or not even elevations but patients in the upper level of CRP levels as they may relate to cardiovascular events?

DR. JOSEPH-RIDGE: We did not draw CRP in the clinical trial. We looked at flare rates but as far as CRPs in the study, we did not do that.

DR. CUSH: I believe these are gout trials, inflammatory arthritis, and you are not measuring an acute phase reactant?

DR. JOSEPH-RIDGE: No, we did not measure CRPs. We measured a lot of other parameters for gout flares, tenderness, redness and swelling, and we did look at flare rate and cardiovascular events but we did not have a CRP measurement.

DR. O'NEIL: You did look at flare rate with

cardiovascular events. Were they correlated? I know the number of events were so small that you probably can't tell.

DR. WHITE: Well, I think that is correct, but there was a distinct attempt to look at levels of urate, resultant levels of urate and flare rates, and there was no relationship between those two parameters and the development of cardiovascular events.

DR. O'NEIL: Dr. Harrington?

DR. HARRINGTON: I want to ask a question of Dr. Cush, if that is okay. I have been sitting here under the assumption, based on the briefing book from FDA, etc., that the efficacy of the drug is not in question; that for rheumatologists lowering the urate is an important intermediate marker. But from your comments over the last few minutes, I am now having doubt about the efficacy of the drug based on the evidence that we have heard. You know, you are making the point, which I think is a very reasonable one, that while urate may go down there are other associated things that happen, in this case acute flares. To get to Dr. Olsen's point, you know, is just lowering urate a good thing for patients with vascular disease? Well, maybe, maybe not as Milton has pointed out.

Now I am hearing from you that in the totality of

what happens to gout patients, do you have some doubt as to whether or not the drug is efficacious? Have they shown enough evidence to suggest that it is or it isn't?

DR. CUSH: Well, I think based on the data they have shown, they have shown that clearly there is a very significant benefit to febuxostat versus allopurinol in lowering serum uric acid. At least, it is twice as potent. However, the data showing attack rates and flare rates were the same between allopurinol and the doses of the study drug in the study for much of the study, and they were very high and they came down, you know, significantly over time but it took a year to get to a point where they became significant.

So, the clinical benefit is marginal but it is there. That being said, you know, I think that these trials are difficult. I can tell you that if I were to look at that and try to extrapolate that to my patient population I would be very frustrated because when I treat gout, both acutely and then chronically, my window of improvement is not going to be a year. If it is going to take me a year to control somebody's gout significantly I think I am not doing all that well.

Maybe I am being a little naive here but we do want to control the uric acid levels, and I do recognize it

takes a number of months to get it down, especially when they start at a very high level. But, you know, I would have expected for a drug that is twice as potent at lowering serum uric acid that we would have had maybe a commensurate clinical benefit as well, and I am not sure I have seen that in the trials thus far.

DR. O'NEIL: Dr. Glasser?

DR. GLASSER: Yes, I guess to get back to this question, I am ready to answer it and the answer is the strength of evidence suggesting a signal is poor, and the strength of evidence not suggesting it is poor because we are dealing with insufficient information and will be insensitive to when enough is enough.

I think a lot of the subsequent questions and then the final one you will ask is somewhat dependent upon what the postmarketing requirement is really going to be and how much strength it really holds.

DR. O'NEIL: Dr. Furberg?

DR. FURBERG: I have a question for Dr. Cush as well. What is your interpretation of the efficacy of results as they relate to the two dosages we are talking about, 40 mg and 80 mg? Clinically, which one would be more important?

DR. CUSH: Well, I think for me and for most rheumatologists the first and most important indication would be as an alternative agent for allopurinol in a lot of patients when we cannot use allopurinol because of renal insufficiency or other issues.

So, in that regard, the 40 mg dose is acceptable as an alternative, meaning that it seems to perform as well as allopurinol in lowering serum uric acid levels and even flare rates. So, in that regard I would be happy with the 40 mg. The 80 mg I think is better at serum uric lowering and that also has some value but I am okay with the 40 mg dose. The role of the 80 mg dose I think has to be determined or higher dosages, say, have to be determined.

DR. FURBERG: So, has the added value of 80 mg been documented to your satisfaction?

DR. CUSH: If the benchmark here is serum urate lowering--and, you know, everyone treating this does look at that as an important outcome, but the ultimate outcome really is how many times A patient comes into my office with uncontrolled synovitis or tenosynovitis. Again, I am not sure there is a much greater benefit there.

DR. FURBERG: Thank you.

DR. O'NEIL: I would like to ask Dr. Olsen to

address some of those questions.

DR. OLSEN: Well, I am also a rheumatologist and I think there are a couple of things to think about. First of all, in terms of patients whom we see, you have to remember that those of you who are in cardiovascular disease, if you see some of our patients you are seeing, like, an end of a spectrum and we don't see patients like that all day. We send them to you guys.

So, I am agreeing that the evidence here is a little bit iffy in both directions, but I was relatively impressed, as a person who does clinical trials, that the illness index of the persons who were enrolled in these trials was relatively high. But I think it is true for all clinical trials that you have to remember for all the drugs that we have that have been approved. We test them under these kind of controlled conditions and then, when we release them they are in uncontrolled conditions and that is when we find out other things, and that may be the same with this drug.

But in terms of getting people in who have a reasonable amount of risk, I mean, for a rheumatologist, and we are not even here speaking for the primary care physicians who take care of most of these people, they were

relatively risky.

Now, what Jack is saying I kind of agree with, except that I think we would all say as rheumatologists that the number of patients that we have seen whom we have successfullyB-because I give the lecture that you have to keep coming back until you get your uric acid down to this number and then you will have fewer of these attacks because that is what we are taught. I hardly have ever seen it, maybe because they can't comply or because the drug isn't that great. But it is what we are taught and it is the thing we have to hang our hats on, and that we hope they will get better.

I was impressed that the tophi got smaller and the amounts of deposits in their joints get smaller. If you saw those pictures, those are the people it is going to take years and years to get rid of those deposits.

So, I think there is quite a bit of evidence to suggest that this may be a useful agent and that we don't knowB-there are still going to be a lot of questions, but it is something that we haven't yet seen. I am always impressed by the fact that gout is the oldest disease we have in our book, Jack, and it is the one we know the least about. Every time you get a bunch of rheumatologists around

a table and find out what they do there is a fight because everybody does something different.

So, the best thing in Phase 4 would be, if there were to be a Phase 4, if we could design some things that would help us answer some of these questions that we clearly still don't know the answers to.

DR. CUSH: Could I just say I too agree that this would be an important addition. Dr. Becker said earlier that he didn't have much hope for allopurinol in the future, and I think that is not necessarily an indictment of allopurinol as maybe an indictment of ourselves and education on proper allopurinol use. Maybe the introduction of a new agent, which may be a better uric acid-lowering agent without much need for dose adjustment compared to allopurinol which may need a lot of dose adjustment to get there--maybe that affords some new opportunities and some better disease control, especially when done by what I will call an amateur population, people who are not as well studied in managing gout or as aggressive in managing it as rheumatologists might be.

DR. NEOGI: I think we should also bear in mind that the threshold of less than 6 mg/dL for serum uric acid is just a biomarker. It doesn't really accurately reflect

the total body burden of serum urate or uric acid. So, people can still have flares even though their serum uric acid is going down. That may just be subclinical tophi that have not yet resolved.

I think the issue for the unmet clinical need for people who have allopurinol hypersensitivity, who have renal insufficiency, who have difficult to manage tophaceous disease this does offer an opportunity. I think we saw that only 18 percent or so in CONFIRMS had mild to moderate renal impairment.

So, although, as Dr. Cush said, we are getting an idea in that population, it would be nice to have more information. I think, to Dr. Furberg's point with the 80 mg, that might be where clinicians might find the 80 mg dosage for those individuals and those with tophaceous gout.

DR. O'NEIL: Dr. Fletcher?

DR. FLETCHER: I just want to thank Dr. Cush who more elegantly summarized what I was attempting to say but didn't do very well about the inflammatory markers.

I would just point out to the group as you discuss it that there are these two time periods that we are talking about, kind of the acute lowering period. The data suggest that when you start these drugs, xanthine oxidase

inhibitors, within a short period of time you can get your uric acid low but the change in the uric acid level can precipitate these inflammatory, systemic inflammatory activities. And, that is what wasn't too clear about whether that might contribute to any changes in adverse CV event rates. So, I think Dr. Cush said it well.

DR. O'NEIL: We have a reply from the sponsor.

DR. BECKER: Michael Becker, University of Chicago. With regard to Dr. Fletcher's comment, I would point out that even between attacks of acute gouty arthritis in over 95 percent instances one can aspirate joint fluid, and the joint fluid shows inflammatory markers. So, it is not only during treatment that one can generate attacks, which can be treated appropriately with prophylaxis, as I pointed out.

But rather than regard the danger to the gout patient of inflammation as arising during the period of three to six months of treatment induced flares, I think we have to think of gout as a chronic inflammatory disease.

The other point I would make is that I tried to portray in the natural history slide that I showed the issue of gout as a chronic, progressive disease. And, I think many of the patients who have the compelling comorbidities that we have been discussing today probably fit far to the

right in that rubric. I think that many of our patients who are early in the course of the disease, who have just expressed a few attacks of gout and are showing signs of having persistent symptomatic disease are going to warrant treatment, and they are going to warrant treatment early to prevent them from getting the inflammatory complications and perhaps even getting attention paid to their comorbidities.

So, I think that I appreciate the concern about what you do with a patient with congestive heart failure who has gout, but there are many, many patients with gout who don't have congestive heart failure and to deny them an agentB-and I will argue this pointBBthat is both a serum urate lowering agent and an agent with proper prophylactic control can result in a decrease in flares over time and a loss of tophus bulk.

DR. O'NEIL: I would like to make one comment. I think we are also forgetting in our discussion of whether we are treating the acute gouty attacks versus the uric acid we have to remember that individuals with chronic hyperuricemia develop chronic renal disease, develop renal stones, and develop a variety of other metabolic consequences that have been mentioned. So, treating the uric acid may not be such

a bad thing. Dr. Packer?

DR. PACKER: Just two point. I really want to emphasize that the heart failure trial that I cited, the point here has very little to do with heart failure. It has everything to do with the fact that this is an adverse cardiovascular signal in a high risk cardiac disease population. And, we have always used heart failure as that signal, and the issues here don't have as much to do with the safety in people with heart failure as the general cardiovascular safety. So, that is one point.

In fact, the sponsor said there is no evidence that xanthine oxidase inhibition carries an adverse cardiovascular risk. Frankly speaking, that is not true. So, I just want to put that into perspective.

But in terms of the strength of evidence, one thing that strikes me is the fact, and I would underscore what Steve said, that the strength of evidence at 40 mg and 80 mg that implicates a cardiovascular risk or absolves the drug of a cardiovascular risk are both poor. The fact is that it is still poor after CONFIRMS. It was poor before CONFIRMS and it is poor after CONFIRMS. That is what is so frustrating.

DR. O'NEIL: Is the FDA satisfied with the depth of

our discussion or is there anything you would like us to address further?

DR. SIEGEL: No, we are okay with that. Thank you.

DR. O'NEIL: Now we will move on to the question of appropriate dosing. In the two Phase 3 trials of febuxostat, 80 mg and 120 mg, the serum uric acid was decreased more in the treatment arms than in the control arm. In the subsequent Phase 3 trial febuxostat 40 mg met the primary endpoint of non-inferiority to allopurinol. The applicant has proposed a dose regimen of 40 mg or 80 mg. Please discuss the efficacy and clinical utility of each dose.

DR. FURBERG: I would like to ask the sponsor why did you give up on the 120 mg dose? Was there a reason for it? Safety concerns?

DR. JOSEPH-RIDGE: No, we did not give up on the dose. When we were in discussions regarding looking at the new study we looked at lower doses of 40 mg and then 80 mg. In the Phase 3 trial previously, actually from the FACT and APEX trial, the 80 mg and 120 mg had similar rates and in some places the rates of cardiovascular events were a little bit lower with the 120 mg.

We decided simply to pursue 80 mg and 40 mg now

and then take a look at what doses are approved. If both are, look at where would the best need for that high dose of 120 mg, what patient population would that best serve, would that get the best clinical benefit.

DR. FURBERG: I mean, if I were to develop a drug I would go for a higher dose as more effective in reducing whatever you hope to reduce, rather than backing off and looking for another sort of Ame too@ drug.

DR. JOSEPH-RIDGE: The 40 mg is similar to allopurinol but the 80 mg, which had been the dose in the prior Phase 3 studies, is a good dose, as you see with the response in serum urate level. You get approximately about 15 percent more additional benefit with the 120 mg. But right now we wanted to make sure that we met some of the questions that the FDA had, look at the two doses, with 80 being a very good dose, and also 40 mg being similar to allopurinol.

We will discuss with the regulatory agencies in the future where would the 120 mg be best utilized, in what patient population, what subpopulation would it really help to have that higher dose.

DR. O'NEIL: Am I to attribute the silence to the fact that Dr. Packer left the room? Or, is there unanimity

of sentiment on the dosing?

DR. CUSH: I am okay with the dosing. I think, again, 40 is non-inferior and looks the same as allopurinol, and 80 certainly was superior as far as serum uric acid and maybe attack rates after a year. I am okay with those doses as proposed.

DR. CLEGG: Yes, I agree with Jack. I think we have had a lot of discussion about allopurinol 300 sort of being under-dosing generally and the 40 seems about that. But the dosage seems fine.

DR. O'NEIL: All right. Then I think we will move on to the third question.

DR. CUSH: One more thing, if 40 is equal to 300, and Nancy pointed out earlier too that we are not doing all that well with 300, it certainly would be advantageous in the management of gout and patients with hyperuricemic disorders that a higher dose be available as well.

DR. CLEGG: But even better, it presents a potential time of education for people who treat gout that 300 might not be the one size fits all dose. So, we can educate beginning at early treatment of gout rather than at febuxostat.

DR. O'NEIL: Dr. Olsen?

DR. OLSEN: And we have a reasonable serum marker to follow so you have the availability to start at one dose. If you don't achieve your goal, then you have another dose.

DR. O'NEIL: Dr. Glasser, you seemed to have a question and then it seemed to fade.

DR. GLASSER: Well, it is bothering me and I don't know why it is bothering so much but, I mean, to compare a dose of a drug with an inadequate dose of another drug and say they are equally effective just bothers me. It sort of reminds me, in the hypertension field, of talking about diltiazine being an ineffective antihypertensive when it was used at a dose that was too low to be effective.

You know, the fact that people are not using a drug correctly doesn't, I think, allow one to say that they are equally effective.

DR. CUSH: Well, 300 is not an effective dose.

DR. O'NEIL: It is effective in 40 percent of patients.

DR. GLASSER: It is not optimally effective.

DR. O'NEIL: But it is optimal for 40 percent.

DR. CUSH: But it still is, you know, the biggest selling dose that is out there.

DR. GLASSER: So is diltiazem 180 but that doesn't mean it is the right dose to use for hypertension.

DR. CUSH: I didn't know that till now. Thank you.

DR. O'NEIL: Dr. Fletcher?

DR. FLETCHER: Just one other point. The sponsor did provide some data suggesting in patients with mild to moderate renal insufficiency that the 40 might even be a bit better than allopurinol because of the need for dose reductions. So, that is another potential benefit I think I would see with the 40.

DR. O'NEIL: What a beautiful segue. I couldn't have paid anyone better for that. The next question is regarding specifically special populations.

For patients with renal impairment it is recommended that the dose of allopurinol be reduced to avoid accumulation of the drug and its metabolites. This practice often limits the ability to achieve target levels of uric acid with the use of allopurinol.

So, the questions posed to the committee are to please discuss whether patients with renal impairment represent an unmet medical need population for uric acid-lowering therapies.

Then secondly, the safety, efficacy and clinical

utility of febuxostat in patients with renal impairment.

DR. GIBOFSKY: I think we will come back to the $64,000 question next but, yes, patients with renal impairment do represent an unmet medical need for uric acid-lowering therapies. As we have heard, lowering uric acid does appear to have some importance. I am not quite ready to walk away from here thinking that lowering uric acid does nothing for cardiovascular risk just yet on the basis of the studies cited.

So, in an individual in whom I can't achieve a lowering of uric acid with conventional methodology because of their renal impairment, then, yes, that would be an important population.

The allopurinol intolerant or the allopurinol resistant population is I think the greater unmet need for us because at the present time we do have the ability to meet their need with allopurinol.

So, I think the real question becomes whether there is a need for an agent to treat the entire universe of gout patients or hyperuricemia patients, or just those who have the unmet need. We have not said anything, because the sponsor has appropriately, I think, excluded people with secondary hyperuricemia. In our institution we are

frequently called on to see individuals who have tumor lysis syndrome and high purine and metabolic pathways because of chemotherapy. And, I think that is another population we have to be thinking about as well down the line.

DR. O'NEIL: Dr. Harrington?

DR. HARRINGTON: Can you help me understand from the epidemiology of gout what actually is the percentage of patients with renal impairment? With all these large studies that have been done, somebody must haveB-what are we talking about here in terms of the percentage of the population with gout that have, let's say, classic creatinine clearance above 90, 60-90, 30-60, and then less than 30. Are those data available?

DR. CUSH: The only data I came across in my review is that, obviously, hyperuricemia and gout were both associated with higher rates of renal insufficiency in those different levels, but a number I don't know. I can tell you that if you go to a rheumatologist's office, a high participant of patients we see are patients with renal impairment. But those are the difficult to manage gout patients who end up in our office, just like the same difficult to manage gout ends up in your office.

I mean, it is probably a substantive number but

the number that is out that is going to emergency rooms or going to a primary care doctor, it is probably not the majority. I don't know, maybe Dr. Becker might know.

DR. GIBOFSKY: Dr. Welton perhaps.

DR. WELTON: Thank you, Dr. Gibofsky. I was poised and ready to spring at any moment so thank you for that.

First, may I point out to the committee that for those who have known gout, particularly having it for several years, the incidence of renal stones is about 25 percent. Of those 25 percent who have renal stones, approximately one-half of the stones will be uric acid in nature.

I can today show you two things that we have done in the FOCUS group of patients. You will recall that that is the group that were followed for 5.5 years. So, if I may first come to the issue of renal function, in that group in the entirety it turns out that, in fact, every single one of them had mild renal impairment. They entered in the range of glomerular filtration rate of 67-60.

Now, I have to share with you I think something very useful and important in terms of the importance of chronicity of management of their uric acid. May I have the slide up, please?

[Slide]

Here is the first issue and bear with me as I take a moment or two. For those of you who have come from Florida today, you will probably say these are hanging chads, but we are going to follow five groups in the FOCUS trial, recalling this was 116 patients, and I am going to show you what happened to their renal function over time, and the correlation of that renal function with the efficiency of reduction of their uric acid.

First, on this axis will be increase in glomerular filtration rate. This will represent decrease in glomerular filtration. Here we see the progression over time for the 5 or actually 5.5 years of the trial.

The first thing I bring to your attention is that, unfortunately, in all of us, year in, year out, we have a pure physiologic deterioration of renal function and, many will recall, it is circa 0.8 mL per year. I show that in the first set of bars. It is a linear deterioration from age 30 to age 80. So, it is basically inescapable. That is the background.

Now, on top of that I show here those who had a 3 mg/dL reduction in their serum urate, then going up 5 different cells to those who had a reduction of greater than

6. What we find is that in the ones who required to get to a target level of less than 6 a reduction of only 3. For example, look at this. Their renal function deteriorated at an annual rate that was greater than pure physiological deterioration. The intriguing thing is those who came in with a higher serum urate level, ergo, needed a greater reduction-BI can only speculateB-may have had more monosodium urate deposition in their renal parenchyma, but we find the intriguing thing is that, in fact, there is a trend to initially maybe a slight improvement in renal function or we can say, at best, a maintenance or renal function.

Again, I would say we don't know why this is. It suggests that chronic, careful, constant mobilization of urate from the renal parenchyma may, in fact, eventuate in some improvement of renal function and that this is progressive over time. Because of the issue of needs, if I might have the slide on this cohort and tracking for renal stones?

[Slide]

In this same trial 18 of the subjects enteredB-we all know they have a history of gout. The mean duration was 10 years. What I bring to your attention is of these 18

subjects, they reported having either one or up to, God knows, 20 episodes of renal stones.

Now, 15 agreed to continue for the 5.5 years. This was the interesting thing, all of them titrated to a urate of less than 6, as we know. At the end of 3 years 2 had a recurrence of renal stones and by the end of the 5.5 years we had 1 more subject excreting renal stones. The important issue is that here every single stone was calcium oxalate in composition. There were no uric acid stones; there were no xanthine stones.

Look, I can't tell you what the nature of the stones were at the outset. We can only surmise that maybe about half would be uric acid. We would surmise, on an annual basis, maybe a quarter would redevelop stones.

So, I think these are two vignettes that I show you of renal relevance, the chronic renal functional issue, the renal stone issue that clearly require further study, but at least they all tell us there may be some benefit to the long-term effect of reduction of urate.

DR. CUSH: Dr. Welton, again, in a gouty population the frequency of renal insufficiency at a moderate to severe level?

DR. WELTON: Severe would be at least 10 percent,

25 to 10 percent, but you can be certain 10 percent are going to go on to renal impairment. It is interesting, again, to point out, Dr. Cush, that here, in a basicallyB-well, I won't say unselected group but taking the entire cohort that went to 5.5 years the range of GFR was 60-67. So, using the kidney classification, the K/DOKI classification, we would say yes, this is renal impairment. It is mild renal impairment but it certainly is there.

DR. O'NEIL: So, it sounds like, from the discussion on the two prior questions, that people do feel that this is an unmet medical need, and that our answer to the FDA is that renal impairment is probably a shoo-in for this particular compound, or at least an interest for the use of this compound.

DR. CUSH: Did we see any data that said 40 versus 80 for patients with renal impairment? I don't think we did.

DR. SIEGEL: Dr. Gilbert has a slide showing the efficacy of 40 mg versus 80 mg in the renally impaired population. That was the second of her two efficacy slides.

DR. JOSEPH-RIDGE: I can give you the percents again. It is also in our C-19. This was also in the FDA presentation where we see the benefit of 40 mg and also 80

mg compared to allopurinol.

DR. CUSH: I don't doubt this. This is a mirror of what we saw for non-renally impaired. The question is whether or not we need to use lower doses in renal impairment to protect the kidney function. Higher doses may be hazardous. I haven't seen any data that say that higher doses have an adverse event profile as far as renal outcomes.

DR. JOSEPH-RIDGE: The information, Dr. Cush, that Dr. Welton showed was the 80 mg in the FOCUS trial. This is what those subjects were on with preservation of the renal function. That was 80 mg.

DR. GILBERT: Also, we did look at safety data. We looked at patients with mild and moderate renal impairment and normal renal function, and we looked at cardiovascular events in those three populations and did not see an increase in events in those who had renal impairment.

DR. O'NEIL: Is there further discussion on this point?

[No response]

All right, the next point, the fourth, is something that the FDA would like us to vote on. We will be using the new electronic voting system for this meeting.

You have three voting buttons on your microphone, yes, no and abstain. Once we begin the vote please press the button that corresponds to your vote. You will have 20 seconds or perhaps a little bit longer to vote. After everyone has completed the vote, the vote will be locked in. It will then be displayed on the screen and I will read the vote from the screen into the record.

Next, we will go around the room and each individual who voted will state his or her name and vote into the record, as well as the reason they voted the way they did.

The question we are asked to vote on is do you recommend approval of febuxostat for the treatment of chronic gout? I would ask for discussion on this now. Dr. Furberg?

DR. FURBERG: If we have conditions related to our vote what button should we call? Yes, no or abstain?

DR. O'NEIL: You can vote either yes or no or abstain and state your reason afterward, whichever you are closest to I presume.

DR. GLASSER: But I agree with Dr. Furberg. It does depend. So, I don't know how toB-I mean, I will do it if you insist but it depends.

DR. O'NEIL: You are always welcome to abstain.

DR. GLASSER: No, I don't want to do that.

DR. O'NEIL: It didn't strike me it was your personality. But, nevertheless, I think the question here is, is this drug something that we should recommend approval for? That can be an approval with recommendations for further study. That can be an approval with recommendations for special labeling as well. And, these things can come up in the next part of the question.

So, the first step is to vote on whether we recommend approval. Is there further discussion to that point before we call for a vote? I think we have beaten this poor dead horse. Let us call for the vote then, please.

[Electronic voting]

DR. O'NEIL: My vote cannot go into the record until I guess I have a working microphone, working machine. Now it is all flashing. Do you want just me or everyone to vote again? Everyone vote again, please.

[Electronic voting]

DR. O'NEIL: All votes have been tallied. For the record, the result of the vote is 12 yes, zero no, and one abstention.

We will now go around the room. We will start with Dr. Glasser.

DR. GLASSER: Well, I voted yes and the reason was contingent upon an adequate postmarketing requirements study with some clout. The FDA never answered my question about how much clout is their clout but we will get to that.

DR. O'NEIL: Dr. Gibofsky?

DR. GIBOFSKY: I voted yes, with an adequate postmarketing study, parameters to be defined, safety signals to be examined, and with an indication for allopurinol-resistant or intolerant gout.

DR. O'NEIL: Dr. Cush?

DR. CUSH: I voted yes as well, and would like to see studies regarding the effectiveness and safety in the populations that Dr. Gibofsky has pointed out, meaning those who are allopurinol-resistant or allergic, and also patients with renal insufficiency.

DR. O'NEIL: Dr. Neogi?

DR. NEOGI: I voted yes, but with some reservations. I think although the event rates were low, if we do look at the absolute cardiovascular signal the number needed to harm may be anywhere from 250-400, depending on which event rates we look at, and given the prevalence of

gout in terms of public health implications, the number needed to harm of 250-400 can still be substantial. So, again, I reiterate the need for adequate postmarketing surveillance and further study in the unmet clinical need populations.

DR. O'NEIL: Dr. Hennessy?

DR. HENNESSY: I voted yes. I also think that there should be a requirement for postmarketing safety formal studies, particularly to look at cardiovascular outcomes.

DR. O'NEIL: Dr. Olsen?

DR. OLSEN: I voted yes really because I thought the clinical efficacy was significant and that it weighed heavily in me looking at that risk as being possibly worth benefits that are going to be achieved.

DR. O'NEIL: I am O'Neil. I voted yes, with the caveat that postmarketing studies for cardiovascular risk should be done. But I also feel that the special populations that have been defined merit a yes vote.

DR. STINE: I voted yes, and the reason was that it seemed to have some efficacy, particularly in certain cases, that wasn't met by other currently available therapies. But I do share everyone else's concern about ongoing safety

monitoring and how that will be carried out, and to what degree that will be successful.

DR. O'NEIL: Ms. Aronson?

MS. ARONSON: I voted yes. I was compelled by the unmet needs and opportunity for another option. And, I would like to see more quantifiable markers regarding inflammation, to see CRP levels also watched postmarketing.

DR. O'NEIL: Ms. Lindley?

MS. LINDLEY: I also voted yes. I felt that it provided an option for those who have no options right now, and that the benefits outweigh the risks.

DR. O'NEIL: Dr. Clegg?

DR. CLEGG: I voted yes as well for the unmet need, and look forward to discussing the postmarketing.

DR. O'NEIL: Dr. Harrington?

DR. HARRINGTON: I too voted yes. I think that some of the issues as to the risk still need to be better clarified, and I took the FDA comments that the new legislation provides them with an increasing amount of authority to insist upon such postmarketing trials to really carry some weight with me because I carry Curt's skepticism as to how often these are actually carried out. I do

believe that it is probably going to require some combination of a large randomized trial and a well done observational study, and I hope that the FDA can discuss both of those.

DR. O'NEIL: Dr. Furberg?

DR. FURBERG: I am the outlier. I abstained. I have two concerns. One relates to the package insert and no one has mentioned that. I think we need to be sure, maybe under the heading of a precaution,@ that we point out that we don't have safety information in patients with known cardiovascular disease. It is not known. That could also be a relative contraindication.

I agree with Robert here that the postmarket trials should be of two kinds, one is the long-term trial in higher risk individuals, not just low risk the way they studied pre-approval but higher risk individuals, the real patients who will use it, and a large database following patients started on the drug and follow them for several years to determine the long-term safety.

DR. O'NEIL: Thank you. We have one more discussion point. Some of you have already started to make comments to that. That is, is the dose appropriate, or are the doses recommended appropriate? Then, what additional

studies, if any, should be conducted post-approval to further assess the safety of the product?

We have just heard nicely Dr. Furberg discuss what studies should be conducted post-approval.

DR. FURBERG: Well, I agree with Sean on the need for a large study. I mean, the study that the sponsor did added 4-6, whatever, events and didn't help anything. And, to increase it to 3-5 years may give us, I don't know, 15, 20 events. It is not going to be very informative. So, they need to do a much, much larger study and follow people for maybe even a longer period of time. So, I think that is right. But also, to get the events up, have some older individuals therein and have the sample size enriched with people who have heart disease. So, I would like to see that.

The other one is that large database, following the model from New Zealand, where you register the first users. You can work through a health plan and then follow them for several years and monitor for serious adverse events.

DR. O'NEIL: Dr. Siegel?

DR. SIEGEL: Dr. Furberg, I wonder if I could ask you to be a little bit more specific. Several other people

have also mentioned epidemiologic studies looking at event rates over time in people receiving febuxostat. How would you interpret such a study? Are you looking to see whether there is an increase in events over time, or are you comparing it to historical event rates, or would you use some concurrent control?

DR. FURBERG: I think you are raising an important issue. That is almost the challenge, what is the comparison. I think we have to spend some time on that. I am not prepared to give you an answer right now but that requires careful consideration. You obviously need a control group that is as matched as possible to the users. Then you have to make a judgment but you can also see what is happening over time.

It is possible that there is a delay in development of serious adverse events so you may see after a while that the event rate goes up. So, you may be able to interpret the pattern of events over time.

DR. HARRINGTON: Obviously you are raising the critical question of what the comparison is because if you are just collecting data on a group of patients and you have no idea who you are comparing them with it can be interesting information but not necessarily terribly

informative.

I would at least put forward the notion that what you are interested in is not necessarily treatment specific observational databases but a disease specific observational database that includes, as one of its parameters, the treatments because then, as Curt is saying, you begin to collect in a concurrent fashion what does the population of this world look like, and then begin to understand how do you look at one therapy versus another.

Now, there are obviously multiple issues with this as being a non-randomized comparison, and I think Curt said this morning and I think he is absolutely right, that you need both piecesB-or Milton said it, you need the observational data and the randomized data to be complementary pieces of information and not necessarily distinctly competitive pieces of information.

That is why my recommendation was that you insist upon both parameters, that you have the randomized trial but you also have the long-term observational data, and long-term I think is key here if you are looking for cardiovascular risk.

DR. O'NEIL: Dr. Hennessy?

DR. HENNESSY: Thank you. I think that for a large

simple trial allopurinol would be a very good control group. I think that it doesn't necessarily need to be blinded and that long-term studies can be done at a relatively small cost per patient. For non-randomized studies I think that allopurinol would also be a good reference group.

DR. O'NEIL: Dr. Neogi?

DR. NEOGI: I agree that allopurinol would be a good comparator. I am concerned about long-term observational studies because of confounding by indication. Those that would be on allopurinol may, you know, have less renal impairment and less other cardiovascular comorbidities and that would be a very difficult issue to sort through.

I wonder if we can take some lessons from the biologics registries from RA to try to determine how to look for small event rate risks in a population that already has an increased risk for cardiovascular disease.

DR. O'NEIL: Ms. Aronson?

MS. ARONSON: As far as the question about appropriate dosing, I am remembering there were a number of dose adjustments in the trials. Within the labeling will there be, like, algorithms? Is that what is standard?

DR. CUSH: To dose as well, we are asked to consider 40 and 80, but that is I think because 120 was

withdrawn because of the safety studies that were then just done with the CONFIRMS trial.

But since we learned from the CONFIRMS trial no new information as far as a safety signal-BI mean, we are not 100 percent sure but at least we can't say that there is a safety concern with 40 or 80, does that take 120 off the table? As far as we know, 120 was more efficacious in lowering serum uric acid in over 90 percent compared to the 80 mg dose. I am wondering if it shouldn't still be on the table and, again, going forward look at that as far as a safety signal.

DR. O'NEIL: Dr. Furberg?

DR. FURBERG: One other comment to pick up on what Milton Packer said, I think it is important that the sponsor is doing a true intention-to-treat trial. So, they follow all randomized patients to the end of the study and don't dismiss them one month after they go off medication. We need to do that. If you start withdrawing a large number of people you undermine randomization and your study is not very reliable.

DR. OLSEN: Could I bring up one thing? It is a smaller issue but the other population we are talking about for this drug are people who can't take allopurinol because

they are sensitive to it. They couldn't go into a randomized trial because they wouldn't qualify. So, I wonder if there would be some consideration of some small study to make sure that people who are hypersensitive or sensitive to allopurinol could take this drug.

DR. CUSH: Is there a need for us to vote on what we, as a group, think about whether the cardiovascular safety of febuxostat has been established based on available evidence? I mean, we have heard a lot of opinions. I think there is a prevailing opinion, but does it help to put that to a vote?

DR. O'NEIL: It appears the FDA is good with that.

DR. SIEGEL: I would just say I don't think we have a need for a vote on that. I think that in the first question the intention was to bring out discussion about whether you thought there was a cardiovascular safety signal. But, based on your comments, maybe that wasn't fully brought out and, if not, hearing opinions would be valuable.

DR. CUSH: My opinion from listening to all the discussion is that we are not so convinced that there is a danger here that we are going to stop the drug from going

forward. But, at the same time, we are not entirely assured that there isn't a signal here and we would like to see a commitment to more studies. I think that is kind of what we heard. I assume it is everybody else's impression. If not, then maybe putting it to a vote would clarify that. But I don't know that we need it. I bring it up just for the sake of clarity. With everybody nodding their head, I think we are okay with that.

DR. RAPPAPORT: I do have sort of a clarification question though for Drs. Packer and Furberg. I have to admit I am just not getting the added value of the observational study if you have a long-term outcome study with the cardiovascular endpoint. Could you explain to us what the additional benefit of doing that additional outcome study is?

DR. PACKER: Am I allowed to talk?

DR. O'NEIL: Yes, you are.

DR. PACKER: I have never had to ask permission before. The reason they are complementary is because in general if you do a big randomized trial powered for cardiovascular events, it is great. It is extremely time consuming, especially if you want to put duration into it. You might get the answer five years from now.

An observational study has the potential to give you more events, although you have the concern about confounding which you have to be careful about but there are very good methods to adjust for confounding variables, and you can get that information probably within a relatively shorter period of time.

So, I don't actually view this as being sort of either/or. You need the randomized trial. You will get the observational study along the way. But in order to do the observational study the drug has to be on the market.

DR. ROSEBRAUGH: Could I just follow-up on that a little bit? So, it is not uncommon for us to get an observational study that is opposite of a randomized trial. So, you get the observational study sooner. What do you do with that?

DR. PACKER: Well, you raise a terrific point, and the question is how often do observational studies and randomized trials produce discordant results. As you might imagine, we could get experts in the world together to discuss that and there might not be a whole lot of uniformity of opinion.

I would contend that not all observational studies are equal quality. Some observational studies use a

methodology which is really much better than others. If you do high quality observational studies, my contention is that they are generally, not invariably, concordant with randomized trials. The data in the literature indicates that if you take observational studies and randomized trials indiscriminately they are concordant about 70 percent of the time. If you sort out for quality they are concordant about 90 percent of the time.

DR. ROSEBRAUGH: Let me just push that a little further because I am going back to my training where they always said don't order a lab if you don't want to know the results. So, let's say I am going to get an observational study in three years and I am going to have an outcome study in five years, would you suggest that I would take a regulatory action based on the observational study at three years, or would I be waiting for five years anyway?

DR. PACKER: The nice thing is when you were told don't order a lab result unless you are prepared to act on it-by the way, a philosophy I agree with, it really does depend on what that lab result was. And, if the observational study, and you are convinced it is methodologically rigorous, shows a worrisome signal you might want to let physicians know about that while the

randomized trial is going on.

Here is the problem. The problem is if people are convinced by that signal it might be harder and harder to complete that randomized trial. Let me put it this way, the observational studies are going to be done, whether the sponsor does them or the FDA requires them, because the drug is going to be in the public; the administrative insurance databases are going to be available. The question is not whether people can do it. The question is can they be done well. I don't know if I answered the question.

DR. O'NEIL: Dr. Hennessy?

DR. HENNESSY: This is going to a new topic. Is that okay?

DR. O'NEIL: Sure.

DR. HENNESSY: Apparently there haven't been cases of severe hypersensitivity reactions to the new drug like there have been with allopurinol. On the other hand, the number of patients that have received it has been a lot smaller. So, I would just want to make sure that we are not overly optimistic about the lack of events when we have too small a denominator and that, at least until we have a bigger safety database, that not be touted as an advantage over allopurinol.

DR. O'NEIL: Dr. Furberg?

DR. FURBERG: To answer your question about the observational study, I worry about the impact of eligibility criteria on participation in a trial. Typically, you exclude 60, 70, maybe 80 percent of people with the condition when you apply your entry criteria. So, the information you have is on a small subset of people with the condition.

I think a register can give you important information on those who are not eligible. So, I can see a comparison between trial eligible from the register to non-trial eligible. I think that would help you interpret the findings and give you some confidence in your decisions.

DR. ROSEBRAUGH: I really appreciate that comment because there has been, particularly with safety meetings, a thought that we should loosen up the eligibility criteria and say why not make it all-comers. Would that give you some reassurance if there were limited eligibility criteria?

DR. FURBERG: Philosophically, I am for wide windows, very few eligibility criteria, because if you have tight criteria the findings apply to that group you have studied and you don't know how to extrapolate, and you may have to do a second study to answer that question. So, it

is much better to have wide windows and take as many comers as you can and then you are much better off. But I am saying, at least in theory, comparing eligible to non-eligible may be useful.

DR. RAPPAPORT: There is one more elephant out there, which is the opposite of what you addressed before. If you have a good randomized-controlled trial that takes all-comers and is going for five years, and you have an observational study and at three years you see that there is a benefit at the end of your observational study and there is not an increased risk, would you suggest at that point that a regulatory action be taken?

DR. PACKER: I don't know what regulatory options would be available to you but, remember, it is not as if these trials yield only information at the end of the study. A trial like this which has I don't know how many patients is going to have a data safety monitoring board. That data safety monitoring board is going to be looking periodically at cardiovascular events because that is actually the right thing to do.

They are going to be aware of the results of the observational study and you can interact with them and, you know, take a look at what is going on in the clinical trial

and the observational study. It is not a black box for five years. So, I just want to emphasize the fact that it is not like you start the study now and you get absolutely nothing for five years. Actually, someone is looking at that data on a periodic basis and that is in the patients' interest and in the community regulatory interest.

DR. RAPPAPORT: And I recognize that. I think the question goes more to at any point there may be a discrepancy between the two studies. If there is a strong negative signal you are probably going to want to act on that and hope that it is confirmed. But if it is the other way, then we have two things and we are not sure where to go and I guarantee we are going to get pressure from somebody to do something about it.

DR. HARRINGTON: But in part it gets to the issue that I think some of us have pointed out. We don't want to see a trial delayed. In other words, the sooner we can get a trial going in this indication, the less likely will you have to grapple with discordant results because the trial will be well underway.

The problem frequently is, as you know, that a commitment is made to do a trial. A lot of foot-dragging goes on. The next thing you know the drug has been on the

market for three, four years. Then clinicians say, well, gee, I couldn't possibly randomize my patients, which is I think what one of your concerns is.

DR. RAPPAPORT: I should add, in response to the question from Dr. Glasser that we never actually got, which is that we do have some authorities now that allow us to put them on a timeline. It is no longer an option to drag their feet. So, once we decide what the right thing to do is we will set up the timeline and make sure it gets done quickly.

DR. PACKER: The other maybe good piece of news, maybe it is not a good piece of news, is that the point at which you get the answer from the observational study and the point where you get the answer from the randomized trial is not likely to be all that distant from each other.

Here is the reason why. To do the observational study, drug has to be on the market. A certain number of people have to be exposed. You have to keep them on treatment long enough to actually be able to meaningfully look at cardiovascular events. So, if it is a cohort study the duration of on-treatment over a period of time, you know, you may get the two within a year of each other. So, it is not as if one is coming out at one point in time and the other one is coming out three years later. I actually

think they will probably be in fairly close proximity.

DR. O'NEIL: Dr. Cush and then Dr. Glasser.

DR. CUSH: For Dr. Packer or anyone who wants to answer this, when we are talking about observational studies, are we talking about just a prospective registry, or are we talking about analysis of administrative claims from managed care?

DR. PACKER: I am not talking about a registry. You need a comparative group. You need two groups, one on drug, one on allopurinol or it could be on whatever, well characterized, with the confounders well characterized in both populations, and in the absence of the comparator the data are going to be very hard to interpret.

DR. O'NEIL: Dr. Glasser?

DR. GLASSER: Yes, two things. One is that I understand the intent of your question but, you know, designing a study takes months of solid work with experts and then you still make the wrong decisions. So, it is not something we can just template to you now. We can give general guidelines but, you know, we have to sit down and really look at the data and, you know, brainstorm. So, it is hard to give specifics and I think that is what Dr. Furberg was referring to.

The other issue is I know you have more clout now. What I am not clear on is what is that clout. I mean, here we may be talking about, I don't know, maybe a $50 million a year drug. So, if your fine is $100,000 for dragging their feet, you know, a company can say that is not worth it. So, what is the clout? I presume you can mandate them to remove the drug from the market but, as you know, once it is on the market that is difficult to do. So, what really are you saying when you say you have clout?

DR. ROSEBRAUGH: So, nobody has tested us yet, and what we have threatened them with is to say it is substantial. I think your point is very well taken. So, if they have a study that costs millions of dollars and they just say, well, I am only going to get fined ten bucks, why get too concerned about it, I would be hopeful that when we do get the test case that substantial will mean substantial so it will not be a problem.

The one thing I would tell you though is that when we have been setting these timelines people have made them and they have been pretty strict timelines.

DR. O'NEIL: Dr. Neogi?

DR. NEOGI: I was just going to respond to Dr. Cush's question. I do think that it is essential to have a

comparator group. And, on the issue of confounding indication, there are more sophisticated analytic techniques so as long as the information is collected appropriately we have the appropriate analytic technique. My concern is, just as we have seen in RA with the question of lymphoma, infection, etc., that we really need to have the advanced analytic techniques to address those difficult questions, and a way to track the people who are on febuxostat, along with the appropriate comparator group.

DR. O'NEIL: Dr. Furberg?

DR. FURBERG: To come back, Steve, to your question about fines, yes, the fines are substantial and they also escalate every month. So, if you miss it, next month you may have twice the amount and then it goes up again. That sounds a little bit scary. But, on the other hand, we have to understand that the fines are passed on to the consumers because they raise the price. So, it is not hurting anyone; it is just passed on to consumers who suffer side effects maybe and also have to pay a lot for the drug.

DR. O'NEIL: Dr. Fletcher?

DR. FLETCHER: I would just like to make a comment, since I am the industry representative, in terms of fair balance. I agree with all of the general comments that this

drug is probably going to be useful and should be studied post-approval. But you have to balance the value and cost of some of these longer-term studies.

I think we have to be sure that it is done in a way that doesn't take so much time or is so expensive that it is not going to be practical to do that. I mean, you could do a very, very large study and I think it is not in any sponsor's interest to have a drug that is not safe on the market long term. I think they do want to understand, as best as possible and within reason, you know, the safety of their drug. I don't see the value of having that out for a few years and not being able to demonstrate that it is efficacious and, particularly, safe. So, I realize it is a very difficult thing but I think you have to balance those two approaches.

DR. O'NEIL: Dr. Stine?

DR. STINE: The only reason I am not jumping up from the table and screaming and yelling about observational studies is that I think once you approve the drug it is going to be very, very hard to compel someone to do a long, multi-year, many thousands of people randomized trial. It is a very, very expensive proposition. It is going to be hard to manage; hard to make sure that that continues on

successfully.

If there is no time advantage to doing the observational study, and we are not talking about something that is as simple and as inexpensive to manage as a registry, then I really can't see the advantage of the observational study. I really don't see that, other than that it is cheaper to run and to supervise.

But if somebody were to show me results from an observational study here and a randomized study over here, I am not even going to look at the observational study. That is how much faith I would put in those, and I don't care what kind of analytical technique you use. One of my colleagues is an expert at this, Paul Rosenbaum, and I am still not going to believe that observational study. I don't care what kind of quasi-matched, pseudo-designed experiment you pretend to do, it is either a randomized study or it is not and, to me, that is the gold standard and if we could get that I would much, much rather have that regardless.

DR. PACKER: I wish randomized trials were perfect.

DR. STINE: Just a hell of a lot better than their competitor. That is where I would go.

DR. PACKER: But only if you think of the two as

competing with each other. There is actually a level of peaceful coexistence. You don't believe in peaceful coexistence?

DR. STINE: Not with observational studies.

DR. O'NEIL: I suspect there won't be any at this table.

DR. PACKER: I understand.

DR. O'NEIL: Dr. Neogi?

DR. NEOGI: I was just going to say that in an ideal world if we could, in a randomized trial, study all the individuals that we need to study, that would be great. But I don't think we will be getting the answer in individuals that we need to know about, and we won't have to rely on observational studies for those individuals.

DR. STINE: And that is all I was saying, that the only reason I am not jumping up and down on the table about an observational study is that I don't think we are going to get the right randomized, designed experiment. If we could, that would be the thing to have. Once you approve this drug it is going to be very hard to jam that genie back down in the bottle and say, oh, no, no, no, I meant this randomized study on this special population group and it is going to cost you umpteen jillion dollars. Forget it. It is not

going to happen.

So, I think that is why observational studies are going to be a necessary evil in this, but I am just speaking over here to the FDA folks, saying don't pretend that the observational study has the same information as you would get from the randomized study, were you able to do it.

DR. O'NEIL: Well, I would like to thank everyone for their participation, their lively discussion, and I think we have done a nice piece of work today discussing a difficult question. Dr. Siegel has some further comments.

DR. SIEGEL: Just from the FDA, I want to thank everyone for your participation. These are very difficult issues and I think our approach to these issues is evolving now. What we can learn from large randomized trials and from observational trials is something that we are learning as we go along. But we really appreciate everyone's participation and thank you very much.

[Whereupon, at 3:55 p.m., the proceedings were adjourned]