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by D. Woods

SUMMARY

An FDA advisory committee unanimously recommended the FDA approve Takeda's Uloric (febuxostat) to treat chronic gout – but only if the company is required to do postmarketing safety studies. The panel discussion and FDA comments also made it clear that the FDA will be very sensitive about any safety signals in other gout drugs in development. Thus, it would not be surprising if the FDA requires more safety studies before approving Savient's Puricase (pegloticase), which was recently submitted to the FDA.

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FDA Panel Recommends Approval of Takeda's Gout Drug

Silver Spring, MD
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The FDA's Arthritis Advisory Committee voted 12 to 0, with one abstention, to recommend the FDA approve Takeda Pharmaceuticals' Uloric (febuxostat, TMX-67) to treat hyperuricemia in patients with chronic gout. The panel gave the drug a positive vote with the express caveat that the company does extensive post-marketing studies to show cardiovascular safety. Febuxostat was approved in Europe earlier this year, and it is marketed there by Ipsen as Adenuric.

Many panel members complained that although the FDA presentation showed that there was no evident cardiovascular risk associated with febuxostat, the data were so scarce that they couldn't be sure, especially since there are no long-term data. Dr. John Cush, director of clinical rheumatology at Baylor University Medical Center in Dallas, said, "We're not so convinced that there is a danger here that we're going to stop the drug from going forward, but we're not assured that there is a safety signal here, and we want a commitment to more studies." Some panel members agreed that there is an unmet need for febuxostat and that there are no cardiovascular safety signals in the latest Phase III data. However, the panel wants more data. Panel members stressed that they want to see a large randomized controlled trial and perhaps an observational study or registry in order to see if there are any cardiovascular risks associated with febuxostat.

Implications for Savient's Puricase (pegloticase)

The emphasis on safety will likely extend to any FDA consideration of other gout drugs in the pipeline, including Savient's Puricase. The FDA is expected to be extremely sensitive to any safety problems with new gout drugs. Puricase seems to be extremely effective in nearly half of patients, but there were three deaths on the drug, and eight patients had cardiovascular side effects compared to no deaths and one cardiovascular side effect with placebo. Even though the randomization in the Puricase study was more heavily weighted to drug patients vs. placebo (4:1), the FDA appears to consider the 8:1 cardiovascular events a signal. An FDA official, speaking after the febuxostat panel concluded, said, "If a 4:1 randomized study showed eight events in the drug arm and one in the control, then there is a possible two-fold increase in risk, and that would be something to look at. It would definitely be a signal…The FDA position is that we don't know if there is an increased risk. It may be a two-fold risk, and that is particularly high, especially if there is something like death or heart attack. There would be reason to be concerned. If there were a concern, especially a significant concern, then the company may have to do more studies…We would ask for more studies and strongly suggest to the sponsor that it do a 1:1 study. That would be the best strategy."

Asked what the febuxostat panel's decisions mean for future gout therapies, the FDA official said, "You saw the vote, and one question is, 'What is a study asking before and after approval?'" Regarding the request for postmarketing studies, he said, "I've been here for 12 years, and all the post-approval studies I've been involved with have all been done…I've become optimistic that they can be done if they are designed correctly."

Background on Febuxostat

Takeda asked for U.S. approval in 2004, but two Phase III trials showed a higher rate of overall mortality, mortality from cardiovascular causes, and cardiovascular thromboembolic adverse events in febuxostat patients vs. patients taking allopurinol. Dr. Bob Rappaport, head of the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products in the Center for Drug Evaluation and Research (CDER), wrote in pre-meeting briefing documents, "The new study did not show a cardiovascular safety signal." Based on the FDA's briefing papers, the panel was expected to recommend the drug for approval, and it did.

If the drug is approved, Takeda said that it will conduct a postmarketing Phase I drug-drug interaction study of the effect of multiples doses of febuxostat on the pharmacokinetics of theophylline. Product labeling will contraindicate use with theophylline until that study is completed. Also, the company said that it has a postmarketing pharmacovigilance plan to track safety information.

Febuxostat is a non-purine, selective xanthine oxidase (XO) inhibitor developed to lower serum urate (sUA) levels in patients with gout. An estimated three to five million Americans have gout, which is a progressive and debilitating disease associated with multiple comorbid conditions. It is caused by deposition of urate crystals in joints and parenchymal organs, which can cause flares and tophi (deposits of uric acid in tissues). Management of gout, prevention of flares, and tophi resolution are accomplished by maintaining sUA <6.0 mg/dL.

The most common therapy in the U.S. is allopurinol (typically used at 300 mg QD), another XO inhibitor. Takeda told the panel that there is a need for more effective medications, and there are some safety concerns with allopurinol, such as hypersensitivity reactions. The FDA told the panel that current treatment options are limited and that recent studies have shown that fewer than half of gout patients treated with a typical 300 mg dose of allopurinol achieve the level of sUA needed for effective management of the disease.

The FDA Perspective

The FDA said that it believes febuxostat is effective in lowering and maintaining sUA <6.0 mg/dL. Febuxostat 40 mg has similar effectiveness as allopurinol, and febuxostat 80 mg has a statistically significantly greater proportion of subjects with sUA <6.0 mg/dL at the final study visit than the all-allopurinol group in all Phase III randomized controlled studies. The FDA wrote, "The difference in the absolute rate ranging from 25%-38% for febuxostat 80 mg over allopurinol clearly establishes the added benefit of febuxostat 80 mg compared to allopurinol." Febuxostat 80 mg also was effective in patients with more severe disease.

The FDA concluded that febuxostat 40 mg and 80 mg:

- Provide an effective treatment option for patients with hyperuricemia and gout.
- Are effective doses, with the larger dose providing added benefit for patients with more severe disease or comorbid conditions.
- Have an advantage over allopurinol of not requiring dose adjustments in patients with mild-to-moderate renal impairment.
- Are well tolerated and have a similar safety profile as allopurinol.
- Have low cardiovascular events.
- Have less risk in terms of severe rash compared to allopurinol.
- Have benefits that clearly outweigh the risks and support approval of febuxostat for the treatment of hyperuricemia in patients with gout.

The FDA's review of the 2006 data from the two Phase III trials suggested that febuxostat may be associated with a higher risk of cardiovascular events. However, the findings were based on a low number of events. Study F-153 looked at whether a larger study (about three times as many patients per study arm than in previous trials) would show similar results to the two earlier studies. The study compared febuxostat 40 mg and 80 mg to allopurinol 200 mg or 300 mg in 2,269 patients with gout and hyperuricemia. At least 65% of the patients had mild-to-moderate renal impairment.

Study F-153 showed efficacy of febuxostat based on an increase in the proportion of patients achieving sUA <6 mg/dL for the 80 mg dose vs. allopurinol. Efficacy of the 40 mg dose was demonstrated based on a statistical demonstration of non-inferiority to allopurinol. In addition, in the pre-specified subgroup of patients with mild or moderate renal impairment, both febuxostat 40 mg and 80 mg doses were statistically superior to allopurinol.

Study F-153 did not show a higher rate of cardiovascular thromboembolic events with febuxostat compared to allopurinol. The overall mortality rate and cardiovascular mortality rate were not increased. Also, neither the investigator-reported primary and secondary Antiplatelet Trialists' Collaboration (APTC) events nor the adjudicated APTC events were more frequent in the febuxostat arms than in the allopurinol arm.

An FDA official opened the panel meeting by saying that the FDA is concentrating on cardiovascular safety today "because the agency does not have any differences with the sponsor" on efficacy. Two panel members then gave presentations.

An FDA reviewer told the panel that febuxostat is safe and effective for gout. She said that the overall mortality rates in the trials were virtually identical for febuxostat and allopurinol. As for cardiovascular mortality, she said that there were two deaths in the allopurinol group and none in the febuxostat group. There was one death in the febuxostat group that FDA reviewers thought might be included in the cardiovascular death column, but the reviewer said that didn't change the pattern of events, so it was not added.

Although the FDA reviewers found no cardiovascular safety signals, the medical officer added the caveat that they were not able to exclude the risk entirely. The FDA's review division did not identify a pattern suggesting an increased cardiovascular risk with febuxostat in the Phase III study.

The FDA reviewer concluded:

- Efficacy of the 40 mg dose of febuxostat was demonstrated based on non-inferiority to allopurinol in study F-153.
- Review of earlier data suggested a cardiovascular signal, and Study F-153 (CONFIRMS) provides additional information regarding cardiovascular safety with three times more patients per arm than in previous studies, pre-specified cardiovascular endpoints, an adjudication committee, and baseline cardiovascular risk similar to earlier trials.
- Data support efficacy of the 80 mg dose of febuxostat based on superiority to allopurinol.

Febuxostat Safety in Study F-153

Measurement	Febuxostat 40 mg QD n=757	Febuxostat 80 mg QD n=756	Allopurinol 300/200 mg QD n=756
All-cause mortality			
Subjects with events	0.13% (Nss, p=0.374)	0.13% (Nss, p=0.625 vs. allopurinol) (Nss, p>0.999 vs. febuxostat 40 mg QD)	0.40%
Relative risk	0.33 vs. allopurinol 1.00 vs. febuxostat 80 mg QD	0.33	---
Events per 100 patient years	0.29	0.30	0.89
Adverse events			
Subjects with ≥1 primary or secondary investigator-reported APTC events	0.92%	0.53%	1.19%
Primary investigator-reported APTC events			
Subjects with events	0	1 person	3 people
Event rate	0% (Nss, p=0.125 vs. allopurinol)	0.13% (Nss, p=0.625 vs. allopurinol) (Nss, p=0.500 vs. febuxostat 40 mg QD)	0.40%
Relative risk	0.14 vs. allopurinol	0.33 vs. allopurinol 3.00 vs. febuxostat 40 mg QD	---
Cardiovascular death	0	0	0.26%
Non-fatal MI	0	0.13%	0.13%
Non-fatal stroke	0	0	0
Non-fatal cardiac arrest	0	0	0
Secondary investigator-reported APTC events			
Subjects with events	7 people	3 people	6 people
Event rate	0.92% (Nss, p>0.999 vs. allopurinol)	0.40% (Nss, p=0.507 vs. allopurinol) (Nss, p=0.342 vs. febuxostat 40 mg QD)	0.79%
Relative risk	1.17 vs. allopurinol	0.50 vs. allopurinol 0.43 vs. febuxostat 40 mg QD	
Secondary investigator-reported non-APTC events			
Angina	2%	1%	0
Coronary revascularization	2%	0	3%
Transient ischemic attack	1%	1%	1%
Venous or arterial vascular thrombotic events	0	1%	1%
Non-fatal congestive heart failure	3%	0	2%

- Cardiovascular events in the study were few in number, both in total and in individual arms. For events that were seen, the rate was not higher with febuxostat 40 mg or 80 mg than with allopurinol.

Febuxostat Cardiovascular Mortality:
Previous Randomized Clinical Trials vs. Study F-153

Measurement	Febuxostat	Allopurinol
Previous randomized clinical trials		
Number of patients	1,177	521
Cardiovascular mortality	0.25%	0
Study F-153		
Number of patients	1,513	755
Cardiovascular mortality	0	0.26%

- However, statistical analysis based upon calculation of confidence intervals does not enable exclusion of the possibility of an increased risk with febuxostat.

Asked about the 12% of patients who were included in the last Phase III study, the FDA reviewer said that the patients were stratified and did not affect the results.

Expert panel member presentations

Dr. Cush, the rheumatologist from Baylor, gave a clinical overview of gout. He said that the frequency of gout is increasing in the U.S. Hyperuricemia associations include obesity, metabolic syndrome, diabetes mellitus, heart failure, hypertension, hyperlipidemia, and renal disease. Dr. Cush said that gout is "totally treatable and preventable and is largely diagnosed and managed by primary care physicians and ER physicians." He added that very few patients are managed by rheumatologists, and there is a "significant amount of inappropriate management."

Current gout management includes:

- Acute treatment: NSAIDs, steroids, colchicines (oral only)
- Steroids: oral, intramuscular, intra-articular
- Chronic treatment: colchicines, probenecid, allopurinol
- >2-3 attacks/year: initiate prophylaxis (cost effective)
- Probenecid: uricosuric, promotes excretion
- Don't use with chronic renal insufficiency, nephrolithiasis, Tophaceous gout
- Colchicine: diarrhea, decreased polymorphonuclear leukocyte (PMN) motility and activity
- Allopurinol: decrease formation – user with chronic renal failure, renal stones, Tophaceous gout, uric acid >11

Dr. Milton Packer, a cardiologist from the University of Texas Southwestern Medical Center in Dallas and a non-voting member of the panel, talked about the difficulties in interpreting safety data in clinical trials when trials are focused on efficacy, "The clinical trials that you see submitted by sponsors for approval for a specific indication are largely focused on efficacy, and when they design a statistical plan and they identify primary endpoints and secondary endpoints, they specify a limited number of analyses. P-values for safety are very hard to interpret." He also criticized adjudicated trials.

Things Dr. Packer said you need to worry about when analyzing the incidence of adverse events include:

- There are hundreds of adverse events (multiplicity of comparisons)
- Adverse events are spontaneous (non-adjudicated) reports
- Analyses that depend on grouping of events are subject to bias
- Small number of events results in extremely imprecise estimates

Dr. Packer said, "A typical large-scale clinical trial may describe as many as 500 individual terms describing adverse events. If the p-value were calculated for each pairwise comparison, then one would, by chance alone, expect 25 events (5%) to have a p-value of ≤ 0.05 and 5 events (1%) to have $p \leq 0.01$. He added that adverse events are spontaneous (non-adjudicated reports), "(If such events are adjudicated) rules guiding post hoc adjudication are inevitably influenced by knowledge that a treatment effect has been sent. Any bar set by the post hoc process can magnify or dilute the effect. Adjudication is generally not applied to confirm absence of event."

He described the problems of grouping adverse events, "Say you were looking at the incidence of thrombotic cardiovascular events, and there was 1:1 randomization. Say there are five myocardial infarctions (MIs) in the placebo arm of a study and 10 in drug, and four incidences of stroke in placebo and eight in a drug, so now you start grouping MI and stroke because you think they may be biologically related. Then, maybe you actually find the risk of MI and risk of stroke on active therapy is similar to what is seen on placebo, but you still want to worry, so you go to other cardiovascular events, such as unstable angina and transient ischemic attack (TIA), which are clinically- and biologically-related to these. Depending on how you group them, you can say there is a problem, or there isn't a problem. So, it's best to develop a uniform definition of a 'group' before classifying events. Because when the process of developing a definition is started after a concern has been raised, those creating the definition have frequently already looked at the data and know (subconsciously) what kind of definition is needed to capture the events of interest."

Dr. Packer said that the most important thing to worry about is the small number of events, which results in extremely imprecise estimates, "What's wrong with imprecise estimates? These imprecise estimates are fine if the intent is to withhold judgment until more data are collected to make the estimates

more precise, but they are problematic if the intent is to stop and reach a conclusion. But the adverse event data generated in a typical trial is not the result of a completed experiment. Viewed from the amount of data needed for a precise estimate, the adverse event data in a single study represents a snapshot in an ongoing experiment to characterize the safety of the drug…Performing an analysis of adverse events data is akin to interim analyses of primary endpoint data in an ongoing clinical trial."

In order to achieve statistical significance in an underpowered analysis, Dr. Packer said, "The effect size must be extreme, and the estimate must be imprecise. However, the more extreme the effects and the more imprecise the estimates, the less likely the result will be reproduced in definitive clinical trials." He suggested developing an approach to analyzing data in trials with small numbers of events which accurately reflect the true imprecision of the treatment effect estimate and its statistical significance."

Dr. Packer concluded that:

- The findings of controlled clinical trials are most easily interpreted when they represent the primary efficacy endpoint of the study.
- Safety data are subject to many interpretative difficulties, including ascertainment biases and initiated false positive rates due to the multiplicity of comparisons and imprecision of estimates inherent in analysis of small numbers.
- The FDA, industry, and academia remain in a quandary as to how to respond in a responsible fashion to observed differences in reported frequencies of adverse events.

He asked, "If you observed an increased frequency of a serious side effect in a clinical trial, how easy would you think it would be to carry out a trial intended to definitively evaluate this risk?" He warned that in a trial with a small number of events the finding of an observed difference does not prove existence of true difference, and he warned it would be difficult to get patients to participate in such a study.

Dr. Packer rhetorically asked, "Do we need to be so certain when evaluating safety instead of efficacy?...We are strict in reaching conclusions about efficacy because saying that there is a benefit when there is none means millions will be treated unnecessarily and subject to side effects and costs. Some might advocate being less strict in reaching conclusions about safety but saying that there is an adverse effect when there is none means millions will be deprived of an effective treatment."

PANEL QUESTIONS FOR EXPERT PANEL MEMBERS AND FDA OFFICIALS

Adverse event causation. Dr. Allan Gibofsky, a rheumatologist at Cornell University's Weill Medical College, said, "I still have one fundamental problem; I'm not sure how to deal with the notion that the report of an event was not caused by the agent…We can see events reported which can be serendipitous and not related to the drug itself." Dr. Packer answered, "I think that it is impossible, for the only thing I'm looking at is the frequency of an event on active therapy compared to the control. One has to be very cautious about putting any weight on whether the investigator thought the event was related to the drug or not."

Pre-approval vs. post-approval studies. Dr. Curt Furberg, a public health sciences physician at Wake Forest University School of Medicine, asked, "What are our options? Do you request information before approval or post-approval, and what sort of study do we set up?" Dr. Packer answered, "I was asked by the FDA to describe the problems rather than the solutions. I was grateful for that, because if I had to focus on the solutions, it would have been a very brief presentation. I think what we're left with are two driving principles: the first is pattern recognition, which is unfortunately a very subjective process. We have to engage in it, but it is replete with error. I have no problem using it as long as we admit that it is an error filled process. The other thing is that everything has to be risk:benefit. How important is this drug to what we need to do for patients compared to the level of uncertainty we have about its safety? The information gathering process should never stop at that point of view, however."

Trial design. Dr. Furberg said, "The case we have today is that trials go on for six months. But there's not a word about what's happening down the road. If we have therapies for chronic long-term use, I don't think that six months is adequate. Either we need post-approval studies or longer studies." Dr. Packer commented, "The best way to get safety data is to maximize the information for every single patient in a trial. Getting patients in trials is a very challenging, very expensive proposition. So, if you can take a patient who is supposed to be in a trial for one month and you can make it six months, that is far more safety information than if you had to recruit another patient. And some safety issues are entirely time-dependent. So it's both – and it's better for the sponsor to… follow patients longer."

The panel also discussed the usefulness of adjudicated trials, which Takeda relied on in its presentation. Dr. Stephen Glasser, a professor of preventive medicine at the University of Alabama at Birmingham, said that he was involved in two meta-analyses that had to be adjudicated, "When we set up efficacy trials with precise outcomes, we were not so precise with the adverse events. Maybe one of the partial solutions may be in identifying the adverse events so that there is some consistency." Dr. Packer, who had criticized adjudicated trials in his presentation, responded, "Everyone puts the concept of

adjudication at some high level. If you have lousy data, it's hard to shine it up with adjudication…Sometimes you've got nothing valuable to adjudicate. So, you're putting your blessing on rather imprecise information. You want to get the investigator on the phone and ask 'What happened here?' Good luck." Dr. Robert Stine, a statistician from The Wharton School in Pennsylvania, added, "A p-value is a p-value is a p-value...That's the whole point of how it's calculated…The other issues go to what is an adverse event, how is it classified? We have to understand the science and make sure we're measuring the right kinds of information…in the right patients. I'm writing a book about how p-values change, and I think it's not the statistics; it's that the study has changed somehow."

Efficacy and dose. A panel member said, "The efficacy equivalent remains a question to me, not that the drug is not efficacious. My concern is that what's going to happen is that…the most common dose used will be the lower dose. So, from the efficacy standpoint that's a concern."

Concern about too few subjects and underpowering. Dr. Packer was concerned about the small number of patients in the studies presented to the panel, "The trial defined certain cardiovascular events in a certain way, but the one thing that if you really wanted to clarify the interpretation of small numbers of events, the one thing that you'd want would be larger numbers of events. Was there any consideration… about designing it in such a way that you would get more meaningful cardiovascular data, i.e., individuals with higher cardiovascular risk in the study, designing to achieve at least some subsets of cardiovascular events? This was considered a cardiovascular safety study, but it had little power." Dr. Jeffrey Siegel, clinical team leader in the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products, CDER, responded, "The main concern was to see if the signal seen in the previous trials would be reproduced in a subsequent study …On the other hand, we believed it was important to have enough events to be able to reach conclusions…if it turned out that the percent of patients with events were the same or lower. So we recommended to the company to make sure there were enough events to be able to reach conclusions. Unfortunately, this study had quite few events, so it is difficult to reach conclusions."

Cardiovascular safety. Dr. Packer and FDA officials had an interesting exchange.

- *Dr. Packer:* "Did the original protocol have any estimates of cardiovascular events or what the upper bound of the confidence interval might be based on the projected number of events?"
- *FDA official:* "They estimated the number of events they expected to see, and the actual number was far fewer."
- *Dr. Packer:* "In all the conversations, was it assumed that allopurinol was neutral?"
- *FDA official:* "We were not aware of any data that would suggest that the rate of cardiovascular events would be higher with allopurinol."

Patient selection. Dr. Robert Harrington, director of the Duke Clinical Research Institute (DCRI), questioned the FDA about why the patients in the studies presented to the panel did not include older patients with heart disease, "Most of the patients are overweight men, and we're not seeing an older group of patients with coronary disease, with peripheral vascular disease, where these signals might be detected? I wonder where that six months time came up – which is a very short time – for a drug that is going to be taken life-long…With heart failure being the canary in the coal mine, the only way you see these effects is when you start exposing the 65-year-old with multi-vascular disease, and we don't have those patients…Why not?" The FDA's Dr. Siegel responded, "The agency did not ask for a cardiovascular outcome study, which we would have done if we had more reason to believe that the cardiovascular safety signal was real. At the time, we thought that there might be a signal, but there wasn't evidence that there was. We asked the sponsor to repeat the kinds of studies done that had been done before…We didn't particularly insist on people with higher risk. Nevertheless, 50% had risk factors, and perhaps 50% had a previous history of heart disease."

TAKEDA PERSPECTIVE

Takeda presented its case for the need for febuxostat and the efficacy and safety of the drug. The panel had many questions for the company and the physician who ran the adjudicated evaluation of cardiovascular events in the febuxostat program. Dr. Packer took Takeda by surprise when he described a trial of oxypurinol that he said showed a higher risk of cardiovascular adverse events in patients taking the drug compared to control and asked the company if that might change its ideas about cardiovascular risk and febuxostat. Another panel member, Dr. Furberg, was very unhappy with the company's proposed Phase IV trial. Dr. Curtis Rosebraugh, director of the FDA's Office of Drug Evaluation II, CDER, told him that, under its new authority, the FDA can impose time limits on required postmarketing studies and levy heavy fines if the company doesn't meet the established deadlines.

Dr. Nancy Joseph-Ridge, president of Takeda Global Research and Development Center (U.S.), told the panel that there is a medical need for a new treatment for gout, and she insisted that febuxostat does not increase the risk of cardiovascular events compared to allopurinol. She said that the clinical study was reflective of the gout population, and there was "no plausible biological mechanism" for cardiovascular events. A new large Phase III study did not substantiate previously observed apparent cardiovascular imbalance, adding, "The benefits of febuxostat outweigh the risks and support approval for the proposed indication." She said that the company submitted an independent evaluation of all potential cardiovascular events in Phase II and III studies and committed to a

Phase IV clinical outcomes study. The Phase III study followed 2,269 patients and was designed to evaluate cardiovascular events and enroll patients with renal impairment.

Dr. Michael Becker of the University of Chicago, speaking for the company, described gout as a progressive and disabling disease affecting 15 to 20 million people. He made the case for new urate-lowering options such as febuxostat which he said:

- Shows safety and clinical efficacy in all patients with gout.
- Requires no dose reduction in patients with mild-to-moderate renal functional impairment.
- Improves convenience and compliance through once daily dosing.

Dr. Becker cited significant comorbidities that frequently accompany hyperuricemia and gout, including:

- Impaired renal function.
- Metabolic syndrome, including hyperlipidemia, obesity, and diabetes mellitus.
- Cardiovascular disease including MI, stroke, and peripheral artery disease.
- Heart failure.
- Hypertension.

Current urate-lowering management of gout includes maintaining serum urate in a sub-saturating range of <6.0 mg/dL in order to reduce body urate pool, dissolve crystals, prevent/reverse gout symptoms, and progression to disability and impaired quality of life. Dr. Becker said that lowering sUA decreases acute flares and reduces tophus size during the first two and three years of treatment. However, he noted that an increase in gout flares occurs early in urate-lowering therapy, and treatment-initiated flares have an impact on patient adherence to therapy. The mechanism for this is speculative, but he suggested it may be due to "activation" of deposited crystals.

Allopurinol has been available for more than four decades in doses from 100-800 mg/day, but:

- 95% of dosing in the U.S. is at 300 mg/day or less.
- Less than 50% of gout patients reach goal serum urate at 300 mg/day.
- Dosage reduction is recommended with renal functional impairment.
- Minimal randomized controlled trial evidence (one trial, 17 subjects) for safety and efficacy of allopurinol at doses >300 mg/day.
- 20% of patients are intolerant of allopurinol, and there is a rare (<1 in 100 patients) allopurinol hypersensitivity syndrome or severe rashes that can be fatal.

Dr. Joseph-Ridge described Takeda's febuxostat development program, concentrating on efficacy. She said that the pharmacokinetics (PK) show that the drug:

- Is rapidly and well absorbed.
- Is dose proportional.
- Does not accumulate (half-life is 5-8 hours).
- Has extensive hepatic metabolism.
- Is renally excreted.
- Can be safely administered with colchicine, indomethacin, naproxen, hydrochlorothiazide, or warfarin.

The company conducted six Phase II/III studies of febuxostat doses from 40 mg to 240 mg. The newest study, CONFIRMS, was a six-month, double-blind trial comparing febuxostat 40 mg, febuxostat 80 mg, and allopurinol 300 mg or 200 mg. The primary endpoint for all the studies was the proportion of subjects with sUA <6 mg/dL at the last three visits (FACT and APEX trials) and the final visit for patients in the CONFIRMS trial.

Efficacy of Febuxostat at Final Visit by Trial

Trial	sUA <6 mg/dL		
	Febuxostat 40mg	Febuxostat 80mg	Allopurinol
CONFIRMS	45% (n=757)	67% (n=756)	42% (n=755)
APEX	---	72% (n=253)	39% (n=263)
FACT	---	74% (n=249)	36% (n=242)
Dose-ranging	56% (n=34)	76% (n=37)	---

Two of these studies were long-term, open-label, extension trials (the Phase II FOCUS trial and the Phase III EXCEL trial). FOCUS is following 116 patients for five years, and EXCEL is following 1,086 patients for three years. In these two studies:

- 80% maintained sUA <6 mg/dL on febuxostat.
- Majority remained on 80 mg.
- About 50% switched from allopurinol.
- Tophi resolved in about 50% of subjects after two years.
- Gout flares declined over time.

The company's efficacy conclusions were:

- Febuxostat 40 mg and 80 mg effectively lower and maintain sUA <6 mg/dL.
- 80 mg superior to both 40 mg and allopurinol, including subjects with high sUA or tophi.
- Both 40 mg and 80 mg effective in subjects with renal impairment without dose adjustment.
- Maintenance of sUA <6 mg/dL demonstrated decreases in gout flares and tophi resolution.

Dr. Joseph-Ridge gave a safety overview:

- 4,072 subjects were exposed to febuxostat doses of 10 mg to 300 mg, with the greatest number of patients at 40 mg, 80 mg, and 120 mg.
- Subjects enrolled were representative of the gout population, with multiple cardiovascular comorbidities and risk factors, including >50% of patients with renal impairment.
- Long-term treatment is being evaluated up to five years.
- The drug has a well-characterized safety profile.
- Discontinuation rates were greater in the 120 mg and 240 mg groups, mainly due to gout flares.

Treatment-emergent adverse events were ≥7% any group. The most common adverse events were upper respiratory tract infections, musculoskeletal and connective tissue signs and symptoms, and diarrhea. The most common treatment-emergent serious adverse events were coronary artery disorders, pain and discomfort, and heart failure. Other events were primarily in gastrointestinal and varied in frequency. Treatment-emergent adverse events leading to discontinuation (≥8% any group) were higher in the 120 mg and 240 mg febuxostat groups. All were on colchicines.

Dr. Joseph-Ridge pointed out:

- Incidence rates for adverse events, serious adverse events, and discontinuations due to adverse events did not increase over time.
- Types of adverse events and serious adverse events in the long-term extension studies were similar to those in the Phase III randomized studies.
- For discontinuations due to adverse events, there were no trends based on timing or type of event.

Cardiovascular safety

Dr. William White, chief of the Division of Hypertension and Clinical Pharmacology, University of Connecticut School of Medicine, presented for the company an evaluation of adjudicated cardiovascular events in the febuxostat program. He ran the adjudications process for the trials.

The non-clinical cardiovascular safety data, according to Dr. White, showed that XO inhibition is not known to cause cardiovascular adverse events. Non-clinical studies also identified no biological mechanisms for potential cardiovascular adverse events. He said that Phase III trials showed that febuxostat had no effects on blood pressure, glucose, lipids, and weight, adding that the patients were "laden with comorbidities" – half were hypertensive, and there was "a great deal" of obesity, many patients having body weight >300 pounds.

Dr. White said he performed an independent review of the cardiovascular safety of febuxostat at the request of the company, "The adjudication process was done at the request of the sponsor…including an evaluation of all cardiovascular events in the two clinical trials and the extension studies. I was not aware of the outcomes of these clinical trials. Yes, I must have known there was a reason to be doing these, but I had no idea of the outcomes. In the new study, CONFIRMS, there was a cardiovascular endpoints committee put together (two cardiologists, one stroke neurologist)."

He summarized his findings:

- Non-clinical data did not demonstrate any mechanisms for cardiovascular toxicity.
- Clinical data showed no alterations in major cardiovascular risk factors.
- Subjects in clinical program had high risk for cardiovascular events, reflective of a population with gout.
- CONFIRMS did not show any increase in cardiovascular event rates compared to allopurinol.
- No dose-related increase in cardiovascular event rates in combined randomized controlled trials.
- No increase in cardiovascular event rates over time with long-term treatment.

Overall, Dr. White said that 134 cardiovascular events were adjudicated in total APTC and non-APTC cardiovascular event rates by patient years over time. The rates were fairly stable up to 18 months, "As we look across time, especially over the first three years, we see that the event rate per 100 patient years is similar. Allopurinol has very similar rates as well…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 we have a representative population."

Other safety issues

Dr. Joseph-Ridge presented safety data regarding renal laboratory analyses of serum creatinine in the febuxostat randomized Phase III trials. Looking at treatment-emergent adverse events by renal function in CONFIRMS, she concluded:

- Overall incidence of adverse events was similar regardless of renal function.
- A small increase in renal adverse events occurred in subjects with moderate renal impairment.
- Similar findings were observed across all treatment groups.
- The same pattern was observed in the combined randomized Phase III trials.

She concluded:

- Subjects reflective of gout population with comorbid conditions.
- No change in nature of adverse events or increase in frequency over time.
- Overall incidence of adverse events similar across treatment groups, regardless of renal function.
- Hepatic effect similar to allopurinol.
- One serious skin reaction associated with allopurinol.

Dr. Joseph-Ridge noted that the CONFIRMS trial showed that there were:

- No APTC events for febuxostat 40 mg.
- APTC events were low and similar for febuxostat 80 mg and allopurinol.
- There is no underlying mechanism of action for cardiovascular adverse events.
- The drug resulted in no change in blood pressure, glucose, lipids, or weight.
- The apparent imbalance in a small number of cardiovascular events seen in the original Phase III studies were not substantial in the CONFIRMS trial.
- Subjects in clinical trials had significant comorbidities, reflective of the gout population.

As for the hepatic effects of febuxostat, Dr. Joseph-Ridge claimed the percentage of transaminase elevations was low and similar between febuxostat and allopurinol. She also noted that no subject met the criteria for Hy's Law (ALT ≥3xULN and bilirubin ≥2xULN).

As for treatment-initiated gout flares, she said:

- These were a predictable consequence of urate-lowering therapy.
- More potent agents are associated with more paradoxical gout flares.
- Prophylaxis is recommended.

Proposed Phase IV trial

Dr. Joseph-Ridge described the Phase IV outcomes study of gout flares that the company is planning. It would be a randomized, multicenter study comparing the efficacy and safety of febuxostat vs. allopurinol in the prevention of gout flares in subjects with gout. From 3,000 to 5,000 patients would be enrolled and followed for 2-3 years. Randomization would be 1:1. In addition to the impact on gout flares, all aspects of safety would be evaluated to refine the label for febuxostat.

Panel Questions for Takeda Experts and Officials

Efficacy. This was an interesting exchange.

- *Dr. Glasser:* "As a non-rheumatologist, I'm trying to get a wrap around the unmet need. You showed that 40 mg febuxostat is similar to 300 mg of allopurinol, but that isn't the high dose of allopurinol. For what percent of non-responders to allopurinol will this new drug achieve your goal level?"
- *Takeda:* "Our long-term data showed that long-term treatment patients who did have response to allopurinol actually switched and responded to febuxostat. In the long-term, open-label, extension study, of those subjects who switched from febuxostat to allopurinol, only 9% were able to achieve a serum rate of <6. However, if you went from allopurinol to febuxostat, we had 67% of those subjects achieving a serum rate of <6."
- *Dr. Glasser:* "But overall it's not a large percentage?"
- *Takeda:* "Possibly 50% of subjects in the open-label study switched (at the low allopurinol dose) – 170 subjects."
- *Dr. Glasser:* "Since this disease is treated primarily by primary care physicians who tend to use the lower doses …I'd think they would use the higher dose of febuxostat."
- *Takeda:* "There is a very limited use of the higher dose… 80 mg should be used in those who don't respond to allopurinol."
- *Another Takeda official:* "The distribution of allopurinol doses indicates that 95% of patients receiving allopurinol were at those less than 300 mg or 300 mg. I think that a few rheumatologists are using higher doses. Also I think that on average patients who require sUA <6 will require 420-450 mg a day. I have not a lot of optimism about being able to see allopurinol used with the most intensive efforts…Many of us have tried to change the ways of our colleagues, and it's not uncommon to recommend increased doses for patients who have not done well on allopurinol."

Gout flares. This was another interesting exchange.

- *Panel member:* "Why is there an increase of gout flares at the outset of the studies compared to the end of the clinical trials? At the end, it was 10%-15%, and at the beginning it was 30%-40%."
- *Takeda:* "When they entered the study, all were changed to a febuxostat dose of 80 mg for treatment. We think that just the change in urate – the change in treatment – caused the flare."
- *Texas rheumatologist:* "Did you have flares when patients changed febuxostat from dose to dose?"
- *Takeda:* "We don't have that data…The event rates… were of patients in which we had follow-up in that 30-day window. I don't recall that we heard of any events that

occurred outside that period of time. It was probably the patients on 240 mg or 120 mg who got flares."

- *Dr. Tuhina Neogi, an epidemiologist from Boston University School of Medicine:* "On the flares, it looks like the allopurinol had similar rates."
- *Takeda:* "There is a numerical difference but not a statistical difference at the end of one year. We believe in looking at the long-term studies, you have to go out longer, over a 2-3 year period to show that. That's why our outcome study is longer, to show a separation."

Proposed Phase IV study

- *Sean Hennessey PhD, PharmD, from the University of Pennsylvania School of Medicine:* "If the primary concern is cardiovascular outcome, I'm wondering if you 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 you are able to follow?"
- *Takeda:* "Our commitment is to conduct a clinical outcome study and in doing that we could look at all aspects of safety…It's a large trial and robust enough so that we can answer a lot of things. We found quite a few patients who are willing to undergo treatment and look for opportunities to be in a trial…because there hasn't been a lot. And we were able to recruit for both Phase III studies, so I hope we will be able to do that for Phase IV. This trial is our commitment for the clinical outcome study, and obviously we haven't had a chance to discuss it with the regulatory agency (FDA). This looks at clinical outcomes in aspects of safety because this is a new compound. We have been developing febuxostat for more than 10 years, and this is our third cycle, and we are committed to doing this and looking at moving this compound (forward) for individuals with gout."
- *Dr. Furberg:* "If you're going to do it you have to do the study right. You have to answer the questions…I don't care about efficacy as much as safety. You have potential cardiovascular safety issues, and you are not addressing it in the postmarket study that you are suggesting. You're suggesting an underpowered study that is not going to settle anything."
- *The FDA's Dr. Rosebraugh:* "We (now) have a lot more authority than we used to have. There are two kinds of postmarketing commitments. There are postmarketing commitments and requirements. And under the requirements, we have a lot more authority in the design, and we put time limits, and there are penalties…Certainly if we go down that path, I'd like to know more about your thoughts on requirements."

NSAIDs and Cox-2 inhibitors

- *Acting chair Dr. Kathleen O'Neill, a pediatric rheumatologist from the University of Oklahoma College of Medicine:* "I have a question about concomitant prophylaxis during trial and difference in cardiovascular outcome depending on that?"
- *Takeda:* "We had a chance to analyze that, but generally there was no difference in the NSAIDs/Cox-2 patients compared to those who didn't take them. It was a very small number of users but no obvious pattern. However, those who took colchicines had cardiovascular events compared to those who didn't, but they were very low rates."
- *Dr. O'Neill:* "I'd suggest separating the NSAIDs from the Cox-2s because they have very different protective effects."

Miscellaneous comments

- *Dr. Daniel Clegg, a rheumatologist at the University of Utah School of Medicine:* "I'm still concerned about the failures that occurred. If a patient changed doses, they received prophylaxis for a prescribed period of time?"
- *Takeda:* "For those who changed dose, in Phase II they were given prophylaxis for four weeks in the original Phase IIa study and prior to 2002. After that, we realized we had to make the prophylaxis last longer, so open-label patients received another eight weeks. It wasn't until after, when we looked at our data in 2004, that we realized that prophylaxis has to be there for a longer period of time, and after six months we see lower treatment-initiated flares."
- *North Carolina cardiologist:* "What was the breakdown of rheumatologists and primary care?"
- *Takeda:* "It was 30% rheumatologists and the rest primary care providers."

Cardiovascular safety. Dr. Packer brought up a study published a few months ago showing that use of an XO inhibitor in heart failure patients resulted in increased cardiovascular risk.

- *Dr. Packer to Takeda:* "If there were evidence that XO inhibition would cause risk of cardiovascular events, would you be worried about your cardiovascular signal? The reason I ask is that I want to point out the OCT CHF study results – a multicenter trial that was just published. Very frequently when you look at cardiovascular safety, you try to look at high risk patients – patients with lots of cardiovascular risk factors or disease. It's become commonplace to look at heart failure as a patient population. Very frequently you go to patients with the most severe heart disease. This is a trial published several months ago. Patients with heart failure were randomized to XO oxypurinol vs. placebo. There were 400 patients on

1:1 randomization. Duration of therapy was six months by intention-to-treat. There were 31 cardiovascular deaths and heart failure hospitalization in the oxypurinol group and 18 in the placebo group, an 80% increase in risk of cardiovascular death on oxypurinol, with confidence interval from 10 to 3.1. The p-value was 0.0456. This is basically what we had in terms of a randomized controlled trial. We'd think of this as an important signal – that XO inhibition in people with serious cardiovascular disease can increase the risk of cardiovascular events. Does that change your view of your own cardiovascular profile?"

- *Takeda's expert Dr. White:* "I was not familiar with that study and so it's an interesting thing that we all need to examine. In the database for febuxostat there is a strong number of people with heart failure in the study – 22% on febuxostat and 19% on allopurinol. We didn't see inducing of heart failure."
- *Dr. Packer:* "But that is not the issue. Heart failure is the canary in the coal mine. It's so much easier to pick up the signal in a heart failure population than another population for cardiovascular risk…Also, you showed a comparison of risk factors of febuxostat and allopurinol, but not vs. placebo. What were the comparisons vs. placebo?"
- *Dr. White:* "There were only 134 patients on placebo – very short term, unfortunately, so we didn't have an evaluation of that. The analysis was just not worthwhile."
- *Dr. Packer:* "You said that CONFIRMS was non-confirmatory. Although it was bigger, the total number of events in CONFIRMS-1 was small and CONFIRMS-2, in fact, wasn't all that bigger than the total database that existed before CONFIRMS. So, it's not that you can't say what you see in CONFIRMS isn't confirmatory…The point has little to do with heart failure and everything to do with the fact that this is a cardiovascular signal in a high risk cardiac disease population, and we have always used heart failure as that signal…In fact, the sponsor said that there is no evidence that (XO)...carries an adverse cardiovascular risk, and frankly speaking, that's not true. In terms of the strength of evidence, one thing that strikes me...is the strength of evidence of 40 mg and 80 mg to absolve cardiovascular risk are both poor…It was poor before CONFIRMS, and it's poor after CONFIRMS, and that's what's so frustrating."
- *After the lunch break, Dr. White responded to Dr. Packer's questions about the oxypurinol study:* "The impact of oxypurinol on heart patients…that Dr. Packer mentioned had a composite clinical endpoint that had several factors in it, did not change on oxypurinol vs. placebo. The jury is still out on this, and we have little evidence that XO inhibitors induce toxicity or harm."

Non-cardiovascular events. Panel members asked about the large number of events (27) that were adjudicated as non-cardiovascular events. A Takeda speaker said, "We cast a broad net on looking at potential events. It wasn't just in terms of coronary artery disorder. It was broader – syncopy, chest pain, dizziness – very broad. Of the 327 potential cardiovascular events, the majority (~270) were not considered serious adverse events, and patients were not hospitalized or considered life-threatening. When we evaluated, we did not determine they were cardiac in nature. Mild elevation of blood pressure, heart racing, things of that nature, the investigators were exuberant in reporting of cardiovascular events because they had the cardiology worksheet. I had not done that before; we gave a non-cardiac group a cardiographic worksheet to work on, and they focused on that. We probably got a gross over-reporting of cardiovascular events."

PANEL CONSIDERATION OF FDA QUESTIONS

QUESTION 1. ***Safety of febuxostat.*** **Please discuss the strength of evidence suggesting a cardiovascular safety signal for the febuxostat 40 mg dose and the 80 mg dose.**

Panel comments included:

- *Dr. Furberg:* He said that the information before him is very limited, "We have information on the low risk group where the event rate is lower than expected. Also, we have information for only six months or so. The issue is …in the lower risk group up to six months there may not be much evidence of harm. For the rest, I have no idea."
- *Dr. Packer:* "The patients that cardiologists are going to see with gout are not these patients. We have an insufficient database to draw inferences about cardiovascular risk in patients with a cardiovascular disease…One of the things that plague the discussion is whether allopurinol is neutral. I wish we knew the answer to that question. I'm nervous about the canary in the coal mine when we compare this drug to allopurinol. When physicians seek to lower uric acid, they have to use something, and it could be the drug they use every day increases cardiovascular risk. But we have to see whether this drug has a cardiovascular risk that is greater than current therapy or a risk period compared to placebo. It could have a cardiovascular risk compared to placebo, but the comparison here should be with allopurinol."
- *Dr. Gibofsky:* He expressed uncertainty about the data and whether there is enough evidence to show that there is no cardiovascular signal. He asked Takeda about C-reactive protein (CRP) in the study and expressed dismay at the negative answer, "These are gout trials, and you're not measuring an acute phase reaction?"
- *Dr. Harrington to Dr. Cush:* "I've been sitting here thinking that the efficacy is not in question…but…I'm now having doubt about the efficacy of the drug…While urate may go down, there are other associated things that may happen, in this case acute flares. Getting to the point, is lowering urate a good thing? Now, I'm hearing that in the totality of what happens to gout patients, do you have doubt as to whether the drug is efficacious?

Have they shown enough evidence to show that it is or it isn't?"

- *Dr. Cush:* "They've shown a significant benefit of febuxostat compared to allopurinol in terms of lowering serum urate. However, the data showing attack rates and flare rates were the same, which means that allopurinol and the doses of the study drug for much of the study were high and came down, but it took a year before they became clinically significant. So, the clinical benefit is there, but marginal. I'm trying to extrapolate that to my patient population, and I'm very frustrated. My window of improvement is not going to be a year. If it takes a year, I'm not doing all that well. We do want to control uric levels; it takes a couple of months to get it down, but I would expect for a drug twice as potent for lowering urate that we have clinical benefit as well, and I haven't seen that in the clinical trials…Is this an alternative agent to allopurinol? There are patients who cannot use allopurinol. In that regard, the 40 mg dose is acceptable as an alternative. It seems to perform as well as allopurinol at lowering flare rates. The other dose also has some value …I'm okay with the 40 mg dose; the role of the higher dose has to be determined."

QUESTION 2. In the two Phase III trials of febuxostat 80 mg and 120 mg, the uric acid was decreased more in the febuxostat arms than in the control arm. In the subsequent Phase III 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.

There was little discussion, and the committee generally agreed about dosing. Dr. Furberg asked why the company did not ask for approval for the 120 mg dose, and a Takeda official said, "We decided to pursue 40 mg and 80 mg doses now and then look where would the best need for that higher dose – what patient population that would best serve to get the best clinical benefit…The 80 mg dose is a good dose, with more additional benefit for the 120 mg, but right now we wanted to meet the questions that the FDA had."

QUESTION 3. *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, potentially impairing the ability to achieve target levels of uric acid. Please discuss: (a) whether patients with renal impairment represent an unmet medical need population for uric acid lowering therapies, and (b) the safety efficacy and clinical utility of febuxostat in patients with renal impairment.

The acting panel chair summarized: "There is agreement that there is an unmet need and that renal impairment is a possible use for this compound."

QUESTION 4. Do you recommend approval of febuxostat for the treatment of chronic gout? If the answer is yes, what is the appropriate dose, and what additional studies, if any, should be conducted post-approval to further assess the safety of the product?

Vote: 12 YES, 0 NO, 1 Abstention (Dr. Furberg)

The panel voted yes, but with the caveat that stringent postmarketing studies be done.

- *Texas rheumatologist #1:* "Yes, with more studies regarding the effectiveness and safety in patients who are allopurinol resistant and/or allergic and other patients."
- *Epidemiologist:* "I voted yes with some reservations. Although the rates were low, we look at the absolute cardiovascular signal. There is a need for adequate postmarketing surveillance and further study in the unmet clinical need population."
- *Pharmacist:* "Yes. But there should be a requirement for a postmarketing safety study, particularly to look at cardiovascular safety."
- *Texas rheumatologist #2:* "Yes. The clinical efficacy was significant. It weighed heavily in looking at the risk."
- *Acting chair:* "Yes. With the caveat that postmarketing studies for cardiovascular risk should be done. I also feel that the special populations merit a 'yes' vote."
- *Statistician:* "Yes. It seemed to have some efficacy, particularly in certain cases not met by current available therapies. But I have concerns about safety."
- *Consumer representative:* "I was compelled by the unmet needs."
- *Patient advocate:* "It offers options where there are no options now."
- *Utah rheumatologist:* "We need postmarketing studies."
- *North Carolina cardiologist:* "I think that some of the issues as to the risk still need to be better clarified. I took the FDA's comments on new legislation giving them authority to insist upon requiring trials; that carries weight with me. I think it will be a combination of a large randomized trial and an observational study."
- *Dr. Furberg:* "I'm the outlier. I have a concern about the package insert. We need to assure that maybe under 'Precaution,' point out that we don't have safety information on patients with known cardiovascular disease. We don't know."

QUESTION 5. What additional studies are needed?

The panel recommended a randomized trial with a long duration and including more patients with heart disease. One panel member (Dr. Furberg) suggested a registry, and a few panel members mentioned observational studies, including a

randomized trial. It was obvious that the panel wanted to see more data in a sicker population.

Panel comments included:

- *Dr. Furberg:* "Much longer, for a longer period of time. Require that the sample size be enriched to add patients with heart disease. Also, a registry of patients to monitor for adverse events…I think that it's important that there is a true intention-to-treat. Follow them through the trial and not dismiss them a month after they go off the medication."
- *Dr. Hennessey:* "Long-term studies can be done at relatively small cost per patient."
- *Dr. Cush:* "We're not 100% sure, but we can't say there is a safety concern with 40 mg or 80 mg. Does that take 120 mg off the table? That seemed to work better. I'm not sure that it shouldn't be on the table and look at that as far as a safety signal…We're not so convinced that there is a danger here that we're going to stop the drug from going forward, but we're not assured that there isn't a safety signal here, and we want a commitment to more studies."

Dr. Packer and the FDA had an exchange about the added value of the observational studies:

- *Dr. Packer:* "If you do a big trial powered for cardiovascular events, it's greatly time consuming. You might get the answer five years from now. With an observational study, there are very good methods to adjust for confounding variables, and you can get that information probably in a relatively short period of time. I don't view this as an either or. You need a randomized trial, so you'll get the observational study along the way."
- *FDA official:* "What do you do with the observational study? You want it before the randomized study results?"
- *Dr. Packer:* "You could get experts in the world together to discuss that. I would contend that not all observational studies are the same quality. If you do high quality observational studies, I contend that they are generally concordant with randomized trials. If you sort out for quality, they're concordant about 90% of the time."
- *FDA official:* "Let's say that I have an observational study lasting three years and a randomized study lasting five years. Should I wait for five years, or can I make a recommendation after three years?"
- *Dr. Packer:* "It does depend on what the lab result was. If the observational study is methodologically rigorous and it shows a signal, you might want to let people know. But if it gets out, it might be hard to complete that randomized trial…The question is whether they can be done well."

The panel also discussed variability criteria on trial participation, and Dr. Furberg suggested opening the trials to more kinds of patients – to all-comers, "I worry about the impact of the variability criteria on participation in trials. Typically you exclude 60%-70%-80% of people with a condition. A registry can tell you important information, (i.e., trial eligible and trial non-eligible). That will help you interpret the findings and give you some confidence."

The FDA admitted that its new powers when it comes to mandating postmarketing studies has not been tested yet. Dr. Furberg said that any fines levied against companies that "drag their feet" will only be passed on to the consumer, "The fines are substantial and they escalate, so if you miss it, next month you may have twice the amount, and it will buildup again... The fines are passed on to the consumer because they raise the price. It's not hurting anyone. It's passed down to consumers who suffered side effects and also have to pay a lot for the drug."

♦