DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE

DAY I

Wednesday, June 2, 2004

8:00 a.m.

ACS Conference Room
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

Allan Gibofsky, M.D., J.D. Chair
Jayne E. Peterson, R.Ph., J.D., Executive Secretary

MEMBERS:

Jennifer J. Anderson, Ph.D.
Joan M. Bathon, M.D.
Dennis W. Boulware, M.D.
John J. Cush, M.D.
J. Michael Finley, D.O.
Steven G. Geis, Ph.D., M.D., Industry Representative
Gary Stuart Hoffman, M.D.
Wendy W. McBriar, R.N., M.S., C.H.E.S., Consumer Representative

SPECIAL GOVERNMENT EMPLOYEE CONSULTANTS (VOTING):

H. James Williams, M.D.
Brian F. Mandell, M.D., Ph.D.
David T. Felson, M.D., M.P.H.

GOVERNMENT EMPLOYEE PARTICIPANT (VOTING):

Marc C. Hochberg, M.D., M.P.H.

GOVERNMENT EMPLOYEE SPEAKER (NON-VOTING):

Robert Terkeltaub, M.D.

FDA

Brian Harvey, M.D., Ph.D.
Sharon Hertz, M.D.
James Witter, M.D., Ph.D.
Lourdes Villalba, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order, Opening Remarks, Introductions

DR. GIBOFSKY: Good morning and welcome to the first of a two-day meeting of the FDA Arthritis Advisory Committee. My name is Allan Gibofsky, from Cornell University Medical College, and it is my privilege and honor to serve as chair of the committee.

I would like to begin by welcoming everyone here, our colleagues, our visitors and our guests from the public to the first of two days of what I know will be a very spirited and interesting discussion focusing on an old disease and new implications for its therapy in the public good.

I would like to begin by asking the members of the table to please identify themselves for the record and for the public who are observing us, beginning on my far right, Dr. Geis.

DR. GEIS: I am Dr. Steve Geis. I am the industry representative on the committee. I am a now retired member of the community and previously worked in the pharmaceutical industry.

DR. FINLEY: I am Michael Finley. I am Associate Professor of Medicine at Western University College of Osteopathic Medicine, Pacific and Pomona, California. I am a member of the committee and a rheumatologist.

DR. CUSH: Jack Cush. I am a rheumatologist from Presbyterian Hospital in Dallas.

MS. MCBRIAR: Wendy McBriar, Director of Arthritis Services at Virtual Health in New Jersey, consumer rep.

DR. BOULWARE: Dennis Boulware, Professor of Medicine, University of Alabama at Birmingham, and I an a rheumatologist.

DR. BATHON: Joan Bathon. I am a Professor of Medicine at Johns Hopkins University and a rheumatologist.

DR. MANDELL: Brian Mandell, Vice Chairman of Medicine at the Cleveland Clinic, Department of Rheumatology.

DR. WILLIAMS: Jim Williams, rheumatologist at the University of Utah.

MS. PETERSON: I am Jayne Peterson. I am the Acting Executive Secretary of the Advisory Committee meeting today.

DR. GIBOFSKY: Allan Gibofsky, Professor of Medicine and Public Health Cornell University and a rheumatologist.

DR. ANDERSON: Jennifer Anderson, Research Professor Emeritus of Biostatistics at Boston University School of Public Health.

DR. HOFFMAN: Gary Hoffman, Cleveland clinic, rheumatology, Professor of Medicine and Chairman of Rheumatology.

DR. FELSON: David Felson, Professor of Medicine at Boston University School of Medicine and a rheumatologist.

DR. VILLALBA: Lourdes Villalba. I am a medical officer in the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products and I a rheumatologist.

DR. WITTER: Good morning. Jim Witter, from the FDA.

DR. HERTZ: Good morning. Sharon Hertz, I

am Deputy Director for this Division of Anti-Inflammatory and Analgesic Drug Products.

DR. HARVEY: I am Brian Harvey. I am the Deputy Director of the Office of Drug Evaluation V, and it is my pleasure to be the Acting Division Director for this Division.

DR. GIBOFSKY: Thank you, all. Now I would like to call on Jane Peterson, our Acting Executive Secretary, to review the conflict of interest statement. Jayne?

Conflict of Interest Statement

MS. PETERSON: Thank you. I am going to read the conflict of interest statement now. The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a

conflict of interest at this meeting, with the following exceptions:

Dr. Brian Mandell has been granted a waiver under 18 USC Section 208(b)(3) for consulting with a competitor on a general issue. He receives less than $10,001 a year. Dr. Allan Gibofsky has been granted a waiver under 208(b)(3) for consulting and speaking for a firm that has an interest in a competitor. He consults and speaks on matters unrelated to those being discussed at this meeting. He receives less than $10,001 a year for consulting and greater than $10,000 a year for speaking. Dr. John Cush has been granted a 208(b)(3) waiver for consulting and speaking for a competitor on unrelated matters. He receives less than $10,001 a year for consulting and less than $5,001 a year for speaking. Dr. David Felson has been granted a 208(b)(3) waiver because a colleague has a research grant from a competitor to study gout in general. The grant is less than $100,000 a year. Wendy McBriar has been granted a 201(b)(3) waiver for consulting with a competitor on an

unrelated matter. She receives less than $10,001 a year.

Dr. Robert Terkeltaub has been granted a limited (208)(b)(1) waiver for consulting with two competitors. He consults on unrelated matters for one and on an unrelated matter for the other. He receives less than $10,001 a year from each firm. He also speaks for a competitor on gout and receives less than $5,001 a year. Under the terms of the limited waiver, Dr. Terkeltaub will be permitted to make a presentation to the committee and to answer any questions related to his presentation, however, he is excluded from participating in the committee's discussions.

Lastly, Dr. Marc Hochberg has been granted a 208(b)(1) waiver for his consulting with two competitor son unrelated matters. He receives less than $10,001 a year from each firm.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freed of Information Office, Room 12A-30 of the Parklawn Building.

Lastly, we would also like to note for the record that Dr. Steven Geis is participating in this meeting as an industry representative, acting on behalf of regulated industry.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. Thank you. Dr. Gibofsky?

DR. GIBOFSKY: Thank you, Miss Peterson. We are going to have a very full agenda today with a number of distinguished speakers making fascinating presentations. I would also like to ask our colleagues in the audience to remember that we do have a time schedule for the open public hearing at which time, if any of them would like to

offer any comments on the presentations, they can feel free to do so. Please schedule them through the Acting Executive Secretary or through a member of the FDA staff as we go into our deliberative and discussion period.

At this point I would like to introduce once again Dr. Harvey, the Acting Director of the DAAODP, who will offer us some welcoming remarks and introduce the first speaker of the program. Dr. Harvey?

Welcome

DR. HARVEY: Great! Thank you very much and thank you all for being here. I would like to say that I am pleased that under my watch the work of many people, over many years, is coming together for this two-day panel on the treatment of gout, both acute and chronic. Of course, you all have the agenda here and we will be getting to that in just a second.

I would like to say it is my pleasure to be the Acting Director of this Division. I am currently at the Office level as well in the Office

of Drug Evaluation V. I took over back in November from Lee Simon so I have some big shoes to fill. This past fall, when I told my wife that Dr. Simon was leaving and, I said, going to a better place, she said, "oh my goodness, is he sick? Did he die?" "No," I said, "he's going back to Harvard." But I am glad to be here.

As we look over the agenda and we see that we are dealing both with the issues of acute and chronic gout, in my current position I have the opportunity, as an outside activity, to still see patients on weekends as an in-hospital medicine physician. This past weekend--you know, federal holiday, what better way to spend it than working in a hospital! I actually did see a patient with an acute attack of gout. I won't go into any details. I don't want to violate HCFA, but it amazed me that in the twenty years since I have been in medical school the treatment options that we have for this patient, just past Monday, really have not changed much. You know, we have the same basic medications that we had back when I was in

medical school in the '80s.

So, I think we really have an opportunity to here to chart the future and we have the expertise. We have all the important groups represented and I think we can really do a lot to sort of outline future clinical trial designs and sort of a broad overview but also in some nuts and bolts ways on the future of clinical trial designs for both the acute treatment as well as chronic treatment of gout.

In thinking about it, as part of the mission statement of the FDA under the FDA Modernization Act of 1997, affectionately known as FDAMA, it actually outlines what our mission is, and it is not only to protect the patients but it is also to promote patient health, to paraphrase. I think the two days of this panel meeting really represent what that is all about.

So, at this time I would like to thank the committee members, both the permanent members and the consultants. I would like to thank the presenters. I would like to thank the industry

representative and the patient representative for their perspectives on things. Of course, I mean, the reason we are all here is because of the patients. I would like to thank those in the audience for your attendance today because getting information out, education, patient awareness, public awareness is also an important part of that puzzle as well. So, for those who are going to be presenting at the open public hearing and those who are in the audience listening, I think we are all playing important roles and I would like to thank you all for being here.

Actually, at this point I would like to introduce the first presenter, Dr. Jim Witter who is one of our senior medical officers in the Division and a team leader. He is going to give his presentation on uric acid and gout. Dr. Witter?

DR. GIBOFSKY: While Dr. Witter is coming to the podium, could I ask the member of the panel who just joined us to identify himself and introduce himself for the record, please?

DR. HOCHBERG: Marc Hochberg, University of Maryland, Baltimore and the Maryland Veterans Affairs Healthcare System.

DR. GIBOFSKY: Thank you, Dr. Hochberg. Dr. Witter?

Uric Acid and Gout

DR. WITTER: Good morning. Thank you for being here today, taking time out of your busy schedules to help us with the topic today and tomorrow, which is an area that is often ignored in terms of public health, as Dr. Harvey has just alluded to.

So, what we want to do over the next two days is to really tap the resources that we have here and gather input regarding issues that we should consider as we think about clinical trials intended to support the development and approval for drugs that treat gout and/or hyperuricemia.

We will be focusing over the next two days on both the acute situations and chronic situations, somewhat of an artificial divide but we thought it was necessary and was most effective to

do it that way. My comments will be particularly towards a chronic setting.

So gout, what is the problem? Well, as I indicated earlier, it is an important unmet medical need because it causes both acute and chronic pain. In certain settings, in certain situations it can also cause joint and renal damage. There is an increasing incidence and severity that has been noted in the literature over the past few years. Estimates, for example, have it at a little over 8 persons per 100,000 in the U.S. that are affected, with a male to female ratio of approximately 1:6. This increase has been commented on, that it is not related to the overall use of diuretics which is becoming more prevalent in the population as well.

It appears as though gout is presenting itself at earlier age. This is particularly true for males. In females the increase seems to be mostly in the postmenopausal period. There also appear to be, and I think we will hear about this shortly, increases related to obesity, tying into what has been called the insulin resistance

syndrome which, again, is something that we will be hearing more about in a second.

Also as Dr. Harvey had indicated, there are really not a lot of treatment options that are available currently. So, one of the outcomes we are hoping for from this meeting will be that in the future there will, in fact, be more options. But to list them, we have for example non-steroidal anti-inflammatory drugs which, as you know, word at the level of prostaglandins. We have colchicine which work at the level of microtubules. This is available both as an oral and as an intravenous agent. We have allopurinol which works at the level as an inhibitor of xanthine oxidase. We also have probenecid which works at the level of the renal tubule.

As we then transition from a clinical trial to look at the data that comes in-house, what we are interested in ultimately is to write a label. I would like to spend a little time on discussing that. Label claims have various legal and regulatory uses but their primary purpose is to

inform healthcare providers and patients about the document that is underlined, both the documented benefits and risks associated with the product. These claims are intended to then describe the clinical benefit and, in fact, once these are approved, the sponsor can actually promote such claims. What we hope for in any situation is that we have as accurate as possible label because this allows for effective risk management down the road.

We do not at the present time have a specific guidance document for gout. We do for many other areas, as you are aware. But if we did, what should we be thinking through in terms of if we tried to standardize the language in the labels for chronic use, for example? Some of the options may be for treatment of hyperuricemia associated with gouty flares, gouty arthritis, tophi or renal calculi.

On the other hand, in an acute situation or for prophylactic use the label might say for the short-term treatment of uric acid-induced gout.

I will just take a second to remind

ourselves then what is some of the language that is currently available for the various agents that are approved: Indocin, one of the oldest of the medicines maybe that is out there. The label under the indication sections says this is effective in active stages of acute gouty arthritis.

Benemid or probenecid reads for the treatment of hyperuricemia associated with gout and gouty arthritis.

Zyloprim or allopurinol reads the management of pats with sings and symptoms of primary and secondary gout, and has in parentheses, acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy. It also notes in rather bold letters, although I haven't bolded it here, that this is not an innocuous drug and it is not for asymptomatic hyperuricemia, a topic that I am sure we will get into today.

As mentioned, also we have colchicine. This is probably the oldest drug. I believe it was DESI; it didn't go through a formal NDA approval. It has in its language for the treatment of gout,

relieving pain of acute attacks or as interval therapy to prevent acute attacks of gout.

It is almost summertime so I thought it would be appropriate to talk about the activities that go on. In the older days of this field it became clear that the gold standard in terms of looking at this problem was something that has been called the urate pool. So, I thought I would just describe that and discuss that for a second as it may apply to our situation here today.

In this cartoon we have a mechanism to fill this pool, and that is the diet. We have a mechanism to also drain this pool through the urine. These can be impacted in various ways which we will be discussing over the next couple of days. But let's take it that we have the pool at a certain level. What I have drawn here is kind of a wave which represents the serum uric acid level. It is intended to be a little bit bumpy because it is not necessarily static. As every pool does, it tells you how deep it is. So, I have given you some numbers here of 10 mg/dl and 6 mg/dl.

Now, when we have a situation that is appropriate under perhaps, you know, steady state conditions--and this is really a poor man's version of modeling. We have Dr. Meyer Katzper here in the audience who can talk to you more if you are interested in modeling and approaching this situation through modeling, but we have an equilibrium, let's say, with two other compartments of this pool, the joint and a tophus. It may be then that under situations of equivalence or when things are equilibrated that there is a dynamic interplay between these two, with exchanging in both ways. But when the uric acid level then rises, we have a situation that the joint, for example, fills more rapidly and we have then an acute attack. As you can see, I have drawn the arrow going back to the pool to maintain again this equilibrium.

With a tophus it may not be exactly the same situation. There may be mechanisms that can allow this to form but there may not be as effective mechanisms to allow it to be resorbed,

and that may be an issue that become important clinically, especially in clinical trials.

So, as our little friend here is encouraging us to do, let's jump in. In terms of what we are trying to get at today, it is the issue of clinical trials and how we should go about thinking about them. One of the basic and first questions we would want to ask then, particularly in a chronic situation, is about the baseline serum uric acid level.

It is interesting in the sense that the prevalence of gout has been estimated to be 30 percent when the serum uric acid is 10 mg/dl, but only 0.6 percent when it is 7 mg/dl and, yet, there still is in general a poor correlation of serum uric acid to gouty flares. So, this is something that we would like you to comment on.

Also, the issue of prior flares at what we call a target joint, the issue of the number of flares that have occurred at this joint in order to get somebody enrolled in a trial, the severity of the flares at that joint and then how should these

be diagnosed? Should we require that these all be diagnosed by crystal analysis for example? Is it sufficient that a physician makes a diagnosis? Or, is it even sufficient that the patient self-reports? We would like your comment on these topics.

With relationship to tophi, we would like some comment about how we go about distinguishing, for example, from nodules that might occur in RA or nodes that might occur in OA, and the relationship of size in terms of entry into clinical trial.

Renal status is also something that we will be talking about over the next couple of days. So, we would like you to think about the issue of chronic renal insufficiency and how that should be factored into any trials.

Regarding exclusion criteria then, particularly for a chronic situation, we want to make sure that at a minimum we exclude other crystal-induced diseases, or that we make sure that there are no other inflammatory diseases or infections enrolled. We would like you to consider

what we should do with renal status, particularly with use of diuretics; with the issue of co-morbid diseases, as I mentioned earlier about obesity; and any thoughts you may have on special populations such as a transplant population or those with genetic defects. The latter is probably applies more to a younger population, as you are all aware.

In terms of efficacy issues then, we would like some discussion on endpoints and the duration of these endpoints. One of the questions that we are going to be discussing today at length, I would hope, is the issue of whether or not serum uric acid is a valid surrogate or not. I will be discussing more about surrogacy in a second.

We also would like to have comment about the number of gouty attacks, particularly early on in a chronic study--how much, how long should we exclude these kinds of events from the analysis? If the endpoint happens to be tophi, should we be thinking in terms of the size or the number?

In other areas of medicine we have given a lot of thought to the concept of disability and

quality of life domains so we would like you to share any thoughts you may have in this area as well.

Then in terms of duration, how much, how long should each area of the various trials be? For example, if one is looking at the endpoint of serum uric acid, is a trial of 6-12 month duration sufficient? Whereas, if you are looking at tophi, if that is the endpoint, do we need to have something more in the range of 1-2 years?

As I indicated earlier, I would just like to talk for a bit about what a surrogate is so that we are on the same page, so to speak, as we go forward with this area. If you look in the Code of Federal Regulations under 314.510, Subpart H and it has been dubbed affectionately the surrogate approval, it reads as follows: FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic,

pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible mortality.

Now, to dig down and drill down just a little bit more, a definition that we use for a surrogate endpoint is a surrogate endpoint of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives. The idea of a surrogate then is that changes induced by any therapy on a surrogate endpoint are expected to reflect changes in this clinically meaningful endpoint.

There are some caveats to the Subpart H approval process. One of those, for example, is that there is a requirement that the applicant will study the drug further to verify and describe its clinical benefit where there is, in fact, uncertainty of the relationships of the surrogate to the clinical endpoint, or the observed clinical

benefit to the ultimate clinical outcome. It is assumed, for example, that post-marketing studies will usually be under way, that they will be adequate and well controlled, and that they must be carried out with due diligence.

Continuing with caveats a bit later in the CFR, it notes that the FDA may withdraw approval following a hearing if some of the following apply: that a post-marketing clinical study, in fact, fails to verify the clinical benefit; that the applicant fails to perform the required post-marketing study with due diligence; that promotional materials are false or misleading; or other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

So, to give you some idea of surrogates are currently are from an FDA perspective, I have just listed some here--blood pressure lowering; this should say lipid lowering, not lipid lowering agents; the use of blood sugar levels; bone mineral density levels and the HIV load. These are some

examples of currently accepted surrogate endpoints.

So, let me restate my question earlier then in relationship to serum uric acid levels and re-ask the question, are these both valid surrogate endpoints? What I mean by that is when you look at, for example, a change of serum uric acid concentration--let's say you go from 10 to 8, is that a valid surrogate endpoint? Or, is it a valid surrogate endpoint when one approaches and attains a selected endpoint, such as 5 mg/dl or 6 mg/dl? So, we would like some discussion on that point because it is a very important distinction.

Then, in terms of serum uric acid, we also would like some discussion about the issue of precision and, reflecting back to the pool idea, that is, serum uric acid estimates can change, can vary, so should we have multiple values done at multiple times to make sure that we are getting the best estimates of what is going on?

Looking again at the issue of targeted versus non-targeted joints, should they be evaluated together or separately? We would like

some discussion on that.

Then, if tophus happens to be one of the endpoints in the trial, what is the best way to go about looking at that? Is it with some kind of imaging modality such as an MRI, or is a manual method sufficient? And, should it be a percent resolution or should it be a complete resolution?

Some of the design and statistical issues that we would like comment on are the issue of the initial titration to minimize flares. I think we are all aware that in the early period this is a problem so we would like your comment on this. We would like you to comment also on the issue of a placebo control. Should this be, for example, during some or all of the trial? It gives us the advantage of looking at superiority to placebo issues to help us understand the effect sizes for example. Or, should we be thinking more about an active control or standard of care control?

Then we could enter into issues of non-inferiority and that would engender a discussion of how different can the test compound be from the

controlling agent. Obviously, the selection of any kind of active control depends on the drug under development. If you are looking at something that works at the level of the kidney, that is different than if you are looking at an enzyme inhibitor.

We would also like some comment on the dose ranging that we should be looking at to achieve various target serum uric acids, and any comments you may have on the approach. Should we have, for example, a means approach or a responder approach, the latter being very important and used a lot for example in rheumatoid arthritis? Then, any comment you may have on this concept which is evolving of a minimal important difference to get some idea, again, of the clinical benefit.

Co-medications and diet issues, particularly in a chronic situation, can be very important and we would like your thoughts about this. For example, use of low dose aspirin can have an effect on renal clearance; the use of colchicine; and then the concomitant use of NSAIDs or COX-2 agents.

We would also like you to comment on the issue of alcohol use and how we should approach that. For example, is a patient diary a way to go about that? Then, any thoughts you may have on restrictions of diet to standardize.

So, the issue always, particularly for approval, is, you know, how safe is safe? I think it is particularly important for this topic today in particular because generally when one goes and decides that something is going to be employed to lower uric acid levels, this is for the most part a lifelong decision. So, the issue we would like you to discuss today is whether this necessarily has to be a daily long-term use or can it be intermittent, and should we approach that.

We would like you to discuss the issues of co-medications, as I just discussed, for either gout prophylaxis or treatment. For example, is there a possibility that a myopathic result could be worsened if somebody is taking colchicine? We would like any thoughts you have on special populations. I had mentioned earlier the issue of

chronic renal insufficiency.

Then, comments about whether ICH guidelines are adequate in this setting. To remind you what that is, some minimum requirements in terms of patient exposure that we look for when an NDA comes in or BLA. In terms of patients then, it looks something to the range of 300-600 patients for 6 months, 100 patients for a year and 1500 total. We are generally interested in what will ultimately be the highest dose.

So, the better that we have clinical trials designed, the better that we have information in these clinical trials, the better decisions can be made at various different levels. For example, at FDA we evaluate the risks and benefits for a population. You can see in this cartoon that the benefits seem to outweigh the risks. The healthcare provider though also takes that same information as is translated in the label and makes a decision for a patient and, again, in this cartoon it looks as though the benefits are winning. Then the patient, importantly the most

important factor in anything, evaluates the benefits and risks in terms of their personal values. In this case, it looks like maybe this person hasn't quite made up their mind but maybe it isn't to their benefit.

So, there is lots to discuss today and tomorrow and we are looking forward to it. Thank you.

DR. GIBOFSKY: Thank you, Dr. Witter. One quick question, if I may, can you give us examples of agents that have been approved under Subpart H and also agents that have been withdrawn by the agency under Subpart H?

DR. HARVEY: Hi, I will jump in--Brian Harvey. The easy question is that to my knowledge nothing has been withdrawn under Subpart H. There was actually a public hearing a few years back, under the auspices I think of the oncology group, where they actually discussed--Dr. Pasteur? There was a panel meeting, advisory panel, where these various issues were discussed and that is a matter of the public record of what things have been

approved under Subpart H, what has been done post-market and what, if any, actions have been taken by the agency. So, that is all available publicly but, to my knowledge, nothing has been withdrawn under Subpart H.

DR. GIBOFSKY: Dr. Hochberg?

DR. HOCHBERG: Yes, regarding the slide on current state surrogates, specifically with regard to bone marrow density just a question, my understanding is that for a new drug to be approved it has to demonstrate fracture risk reduction, but for a new form of a preparation, for instance, of an already approved drug it can be approved with comparability with regard to bone marrow density. Is that correct, or am I incorrect?

DR. HARVEY: Well, I think the specifics of what other divisions do in their risk/benefit analysis--I would refer you to the various guidance documents and policy documents in those specific areas, and it is an evolving field and, of course, those various divisions go to their expert panels for input as well. So, we are sort of on a

parallel track with them. They may be a little bit ahead, but I think some of those technical nuances really all are on the FDA web.

But you raise some valid points and during your discussion there may be some parallels and sometimes those parallels are valid and sometimes they are not. Of course, today's discussion will be a general discussion about those gout issues but with the specifics of gout that may supersede some of the other areas as well.

DR. GIBOFSKY: Thank you, Dr. Harvey. Are there any other questions from the panel about the methodology? We will talk about pathophysiology throughout the rest of the day. Dr. Geis?

DR. GEIS: Just quickly, is there any history of a drug being approved based solely on a surrogate marker without the sponsor collecting any clinical relevant data?

DR. HARVEY: Brian Harvey, I will keep jumping in because these really are big picture questions you are asking and not really specific for the gout issue. But I think we are all well

aware of the public record in the area of HIV disease and how the approval of drugs in that area have really been tied not only to clinical outcomes but also the surrogate of viral load. Of course, significance is always in the eye of the beholder, but there really is a huge body of information out there in the public record on those various areas. We can look to HIV treatments as one area. Oncological project is another where they have sort of led the field of pharmaceutical development using these surrogate endpoints. Of course, as you know, there is a huge body of clinical literature as well as a lot of FDA information, both in formalized guidance as well as public record from previous panels. So, it is a good question. I think it is a good guiding principle but, as always, significance is in the eye of the beholder.

DR. GIBOFSKY: Thank you, Dr. Harvey. At this point, if there are no other questions from the panel regarding Dr. Witter's presentation, I would like to call up Dr. Robert Terkeltaub, who is Chief of the Veterans Administration Rheumatology

Section and Professor of Medicine in Residence at University of California, San Diego, who will address us on gout as an evolving problem at a therapeutic crossroads. Dr. Terkeltaub?

Gout: An Evolving Problem at a Therapeutic Crossroads

DR. TERKELTAUB: I want to thank Jim for inviting me and also to thank Brian for providing a note to my chief of service so I could be excused from my medical duties. It is a nice break from that particular service right now.

I am really honored to be here. I am going to talk about a problem that I have worked on for many years and that I feel very strongly about as a major public health problem. Basically, we are dealing with the prototypical crystal deposition disease. What you are seeing here, of course, is an aggressive tophus deposited in the toe that is destroying underlying connective tissue.

The issue is partly of the normal metabolism of uric acid, the normal product of

purine metabolism. I am not going to belabor you with all the steps involved in purine metabolism but basically xanthine oxidase at the end stages of purine metabolism generates uric acid and, obviously, this has been a fruitful drug target and allopurinol targets this particular enzyme.

We are dealing with a question of balance and human uric acid balance is pretty precarious because the size of the total miscible uric pool in the typical male is a gram to 1200 mg. Our production and intake of purines balances with our elimination of purines on a daily basis. So, the size of what flushes through a uric pool is about the same size as the uric pool. So, you can see that either excess purine production or even small decreases in uric acid elimination will produce hyperuricemia over time.

Basically, we are dealing with a disease in which hyperuricemia is only one manifestation. We have an increase in the total body urate pool and ultimately the deposition of monosodium urate crystals and clinical expression in these various

forms, including not only arthritic manifestations but also urolithiasis with not only uric acid but also calcium oxalate in some patients, and a rare problem these days in the form of interstitial nephropathy, most likely because of better control of not only hypertension but also hyperuricemia.

So, we have a disease in which the etiology is very well understood vis-a-vis the monosodium urate crystal being pro-inflammatory, depositing tophi, and we understand purine metabolism very well. We have a disease in which diagnosis and therapy are well developed but often poorly applied, which is an issue which hasn't yet been discussed but can be, and we have a common disease in which we have approximately 3-5 million affected subjects in the United States alone. We have a high prevalence in certain minority groups of a disease that is growing in numbers, and a disease that is evolving clinically due to not only socioeconomic factors but also iatrogenic factors that must be considered. So, we have a major public health problem.

If you look at the raw numbers, if you are dealing with the NIH-IS survey and self-reported prevalence, you are dealing nearly with a doubling of the self-reported prevalence of gout between 1969 and 1996. If you are looking at the annual case incidence in this study from Rochester, you are dealing with approximately a 50 percent increase. Now, these epidemiologic data are subject to limitations in a disease that is episodic, that is recurrent but, anyway, it appears from the numbers that the disease is more common.

The reasons for this are complex. One is almost certainly the increased of longevity of the population. Sustained serum uric acid elevation over time times longer time is going to lead to more gout, in our view. An increase in the prevalence of hypertension, increased use of diuretic and aspirin therapy--and I will show you our own evidence but basically the epidemiologic evidence in certain studies argues that increased diuretic use is a risk factor for more gout.

Dietary trends--increased obesity and

metabolic syndrome, demographic trends in the United States, improved survival from coronary-artery disease, congestive heart failure and diabetes mellitus, and many of the patients who have stents wouldn't be around to get gout in this day and age, and basically increased end-stage renal disease and increased survival from this, and increased transplants as well as the limitations in the current generation of anti-hyperuricemic drugs.

So, what are the numbers here? If we look at hypertension alone, there has clearly been more than a 10 percent rise over the 1990s. If we look at hypertension treatment patterns, there has been a major change. I wanted to cite the ALLHAT study which is a study that was done on 42,000 subjects in the United States and compared outcomes, including non-fatal MI and also stroke and CHF, and the results were interpreted to support the use of inexpensive thiazides relative to ACE inhibitors, calcium channel blockers, alpha-adrenergic blockers for the treatment of mild to moderate hypertension. So, this study has been quite influential.

For example, in my own healthcare system, the VA, VISN-22 which is the desert Southwest VA, we have reviewed a population of approximately a quarter of a million and we have a very special group of patients, obviously, about 90 percent male. We are dealing also with about 40 percent of the population in our VISN-22 population being 65 years of age or older. But in this 5-year period that was reviewed, very generously by a pharmacist, aspirin use was up approximately 10 percent. Furosemide use was up approximately 4.7 percent and hydrochlorothiazide use in the cost conscious VA system was up 74 percent. Allopurinol was up 12 percent during this time period. This is in line with national prescribing figures for allopurinol, as I understand them. So, we are dealing with a situation where the hydrochlorothiazide use is exploding in the very cost conscious environment of the VA and most likely cost conscious environments elsewhere, which means almost everywhere.

I saw the movie "Supersize" this weekend and I was very happy to see that hyperuricemia and

gout made it onto the radar screen of that movie. Basically, Time magazine has covered this topic in depth and this week's cover issue is on obesity as well. We are very clear on the fact that obesity is a big problem in America and increased body mass index alone is associated with hyperuricemia but insulin resistance clearly compounds the problem.

The principal features of the metabolic syndrome are legion and they include hyperuricemia. Basically, what we are dealing with is a number of renal effects pure to insulin resistance alone and then compounded by hypertension. But basically hyperuricemia stimulates increased renal sodium reabsorption and uric reabsorption as well. There is an additional mild effect in renal ammonium excretion associated with insulin resistance that promotes an acid milieu. Basically, we realize that the relative risk of urolithiasis in men who carry a diagnosis of gout is at least 2. So, the problems of insulin resistance certainly compound hyperuricemia, and up to 20 percent of patients with gout have a history of kidney stones and this

may also contribute to morbidity with gout.

So, what we are dealing with along the lines of epidemiology is a problem that goes up with aging. The age-adjusted prevalence of metabolic syndrome rises steadily so that up to 35-40 percent of individuals greater than age 70 meet the criteria for metabolic syndrome. You can see when you look along ethnic lines and if you look at men and women that the most rapidly growing ethnic subpopulation, Hispanic subpopulation has the highest age-adjusted prevalence of metabolic syndrome.

Basically, what are the diet and alcohol related trends that may be influencing the incidence of gout? Choi has done a very impressive large study in male health professionals aged 40-75, almost 50,000 people followed up for 12 years, and 730 of these people developed new gout in this time frame. So, these were people who did not have gout at the beginning of the study. The relative risk of incident gout was 1.41 in the highest quintile for meat consumption; 1.51 for seafood;

and then almost half for dairy product consumption, low fat dairy products; and any form of alcohol, 2.53. But when it was broken down to beer, 1.75 for 5 beers a week to 1 beer daily; 2.51 for 2 or more beers daily; and then spirits, 1.15; and wine, 1.04.

Now, you know, I view these data for dairy products as maybe reflecting ascertainment bias given that the people in the highest quintiles for dairy product consumption in this study who had the low incident gout risk were consuming 2 glasses of skim milk per day or consuming a fair amount of non-fat yoghurt per day and there has to be a difference between people who drink a lot of skim milk and other people.

Basically in terms of the multivariate analysis, these differences were not immediately obvious when hypertension diuretic use was factored in and I think people recognize that there has to be a difference between a beer drinker and a wine drinker. So, I think there is also room for interpretation of ascertainment bias in these data,

but these are very compelling studies that are going to have to be addressed.

Basically, we have another issue in that several popular diets that are high in fat and also high in meat and seafood consumption and low in carbohydrates have the potential to promote hyperuricemia by ketosis and high meat and seafood intake. I won't mention these diets by name because I don't have to, everybody knows the names, and people realize that there is a low carb frenzy in this country that also has very high economic impact.

The economic impact also is something that is reflected in beer intake. If you look at the alcohol consumption numbers in the United States, alcohol consumption actually has been somewhat flat or slightly declining over the last 20 years, however, beer consumption--and beer of course contains the very readily absorbed di-tetra purine guanosine--beer consumption is the segment of the alcohol market that has risen steadily. This is the very hot-selling lite beer de jour, Michelob

Ultra, but basically what we are dealing with is lite beer and low carb beers have markedly increased in their market share and in their overall consumption in this country and have been promoted as health-conscious options. They certainly are a bit lower in carbohydrates but they are not lower in guanosine content. So, this is a factor in terms of the public health problem that has to be considered as well if one takes into consideration the data on incident gout that I mentioned.

The other issue in terms of the epidemiology of this disease is that the classic profile of a gout patient, including several people in this room, I am sure, is illustrated here. We are dealing with a disease in which the classic profile is changing. There are many more females that are involved and there appears to be a rise in the 70-80 age group as well.

Gout in older women is increasing in prevalence partly because of increased longevity. That is the assumption, but also it is linked to

very common use of thiazide diuretics and currently the numbers are that more than 25 percent of individuals greater than the age of 65 are using diuretics, mainly thiazides, and also linked to chronic renal insufficiency and congestive heart failure. Attending on internal medicine this month, we realize that about 20 percent of our admissions at the VA are for congestive heart failure exacerbations. So, we are seeing a lot of gout and CHF and a lot of gout in older women with CHF at the University of California, San Diego and at the VA in San Diego.

Will decreased use of estrogens ultimately raise uric acid and gout prevalence? Estrogens are uricosuric and estrogens are becoming somewhat more out of favor given the recent data in press, and there is a question about whether serum uric acid and gout prevalence will rise in women because of the anticipated decrease in the use of estrogens.

Also, gout in women can be different clinically and this has to be factored into the design and interpretation of clinical trials. As

opposed to the classic podagra, the gout in women can masquerade as inflammatory hand osteoarthritis. Uric crystals love to deposit in osteoarthritic joints, most likely because of solubility issues with respect to altered matrix integrity in the osteoarthritic joint. Gout, presenting as tophi is a common presentation in older women with tophaceous gout.

What about renal insufficiency? Renal insufficiency promotes hyperuricemia and gout clearly, and makes management of hyperuricemia and gouty arthritis substantially more difficult. What about the numbers? Well, we know that in 1987 there were 156 new cases per million of end-stage renal disease. In 1997 there were 303 new cases per million. And the prevalence of end-stage renal disease is 4-5 times higher in African Americans and in the elderly.

In terms of transplants, the number of transplants has nearly doubled also in the same time frame, partly because of improved transplant donor networks and protocols. In addition to renal

transplants, we see more heart, liver and pancreas transplants as well. We realize that transplants and cyclosporine-induced gout is an emerging problem in gout. In terms of cyclosporine-induced gout in the setting of major organ transplantation, hyperuricemia is present in more than 80 percent of the cyclosporine-treated patients in this setting. Mean serum urate levels are often spectacularly high and the gout prevalence is between 8-13 percent by 3 years, typically more than 10 percent, and a lot of this depends also on the cyclosporine dosing which often is higher for the cardiac transplant patients.

So, what is going to happen with transplant-associated gout, associated with cyclosporine use clinically is that we see rapidly expanding tophi refractory to therapy. There may be some sort of extrarenal cyclosporine effect that may affect urate solubility. This appears to be beyond the pale in terms of the rapid expansion of tophi relative to the urate levels, and the arthritis may be refractory to steroids and other

anti-inflammatory therapeutics. We often see patients with transplants who are on 10 mg, 15 mg of prednisone a day and still come in with polyarticular gout. Cyclosporine, of course, is nephropathic and induces chronic renal insufficiency, and cyclosporine and chronic renal insufficiency can contribute to serious adverse drug interactions. One of these is called colchicine myopathy which may present very quickly after oral colchicine initiation in this setting.

I have some good news. Cyclosporine and gout will be a brief footnote in the long history of gout. At the VA we looked at cyclosporine prescriptions over the same time frame and we looked at thiazide prescriptions and they were down by approximately a third, and the prescriptions of tacrolimus and sirolimus were way up in that time frame. People are realizing that there are alternatives with less hyperuricemic toxicity but also principally less nephropathic toxicity. These are being currently optimized for transplant medicine and the cyclosporine alternatives include

tacrolimus. Another inhibitor of calcineurin like cyclosporine, however, is marginally better for hyperuricemia as well as hypertension and nephropathy in my view, in reviewing the literature, as well as sirolimus and mycophenolate. Combination regimens with lower dose cyclosporines, such as 25 mg twice a day of cyclosporine microemulsion are clinically efficacious. Eventually, clearly, advances in therapeutic new intolerance will render cyclosporine fully obsolete and we will get rid of any iatrogenic issue.

So, what we have here is the situation of increased gout prevalence and increased clinical complexity of gout in the United States. It is very hard to measure gout clinical complexity but from talking to my colleagues everywhere, people generally agree that gout is more difficult to manage; there is more tophaceous gout and the problem of gout and chronic renal insufficiency makes the disease more complex. This has clearly evolved over the last 20 years and has accelerated over the last 10 years. What we have is a "perfect

storm" so we have to try to deal with the numbers.

The IMS data for the rise in allopurinol-treated patients is impressive. It is 25 percent in this time frame. Basically, it is not because of improved medical education, I am pretty certain.

The other problem is that refractory tophaceous disease has not disappeared and appears to be making a comeback, as I have mentioned. Refractory gout is painful, destructive and incapacitating, as you can see by these erosive changes illustrated here. Joint erosions can progress even with effective therapy that lowers serum urate. Once you deposit urate crystals in a joint, the crystals are very pro-inflammatory and can promote matrix metalloprotease expression and nitric oxide production and promote cartilage destruction and connective tissue destruction. So, we have to deal with this issue.

There are some larger issues here. Sustained hyperuricemia, even in a very predisposed population such as in Kinma, in Taiwan is associated with incident gout in only 20 percent by

5 years, and we need to determine what factors, other than serum urate, account for the clinical crystal deposition as gout, and what are the natural urate crystallization regulators. Can they be harnessed in therapy? In the meantime, we are dealing with measures to reduce inflammation and reduce serum urate.

The extent of effectiveness of the non-pharmacologic mechanisms directed to urate metabolism, such as diet, alcohol, lifestyle and anti-hypertension therapy, are not exactly clear, to be kind. Clearly, the existing generation of anti-hyperuricemics is antiquated and needs improvement.

What about diet because we are the FDA and, you know, this is the Food and Drug Administration? What about diet? Traditional low purine diets that have been used in the past more commonly are unpalatable and they only reduce serum urate by up to 1 mg/dl or 15 percent about the max. What about roles of other diets? There is a customized 40/30/30 diet with caloric reduction.

It was a small open study with 13 patients. These were all overweight or obese men with gout. When you tailor a weight reduction diet for insulin resistance and look at 16 weeks and achieve a lot of weight loss--at 16 weeks you are achieving about 1 lb per week weight loss, which is pretty impressive--urate levels decrease by 18 percent with a 40/30/30 carb/protein/fat scheme. Caloric restriction is the key here, but also replacing refined carbohydrates with complex ones and replacing saturated fat with monounsaturates and olive oil, nuts and seafood. So, this argues that some diets that are the same overall scheme as some of the popular best-selling book low carb diets may actually be okay for gout. So, not all low carb diets may be adverse. The effects of diet and alcohol modification on hyperuricemia and on gouty arthritis itself need a careful controlled long-term study, including the very popular low carb diets right now which really have not been studied at all in a controlled way, although there is a hell of a lot of publicity on the Internet about

gout being worsened by several low carb diets.

In terms of the uric acid lowering pharmaceuticals that are currently in use, allopurinol, in terms of serum uric acid lowering therapeutics, is dominating of course the use in the U.S. market. Oxypurinol has been available on a compassionate use basis and, of course, is a major active metabolite of allopurinol.

Allopurinol has limitations and that is why I think we are assembled here in part. Rash in approximately 2 percent of subjects; intolerance, and we will go over what defines intolerance, in up to 10 percent of subjects. Major allopurinol hypersensitivity is rare, approximately 100 cases reported, but has a 20 percent mortality rate. Oxypurinol cross-reactivity puts some limits on alternative use. Then tophus reduction with allopurinol is often slow so that raises another bunch of issues because the optimum dosing of allopurinol relative to label and relative to the published guidelines for avoiding allopurinol hypersensitivity syndrome is controversial. The

optimum dosing of allopurinol is particularly controversial with chronic renal insufficiency.

If you look at drugs that are used to promote uricosuria, probenecid is the most common one used in the United States.

Sulfinpyrazone use is problematic. Sulfinpyrazone is related to phenylbutazone and can cause some of the same problems that phenylbutazone causes hematologically at the level of the GI tract and also the anti-platelet effect of sulfinpyrazone can lead to adverse drug interactions.

Benzbromarone is not FDA approved and hepatotoxicity can be serious with this drug and has led to withdrawal from the marketplace in France, as an example.

Losartan and fenofibrate are among drugs--every two or three years there is some other drug that is discovered to be mildly uricosuric. The current ones are losartan and fenofibrate which have relatively weak effects and questionable extent of synergy with current drugs but can get in the way in terms of clinical trial evaluation. We

are dealing with drugs that typically will reduce serum urate on their own by 8-10 percent and up to 15 percent or 20 percent.

Can we develop pharmacogenomic approaches to optimize uric lowering therapy based on spectacular recent science in terms of understanding renal urate handling? The classic disorder of renal urate excretion in primary gout is such that if you look at the gouty patients' urinary uric acid relative to their plasma uric acid at a level of, let's say, 8 mg percent of plasma uric acid, the patients with gout will have approximately half as much urinary uric acid put out. Given that three-quarters of patients are under-excreters, this is quite significant.

Basically, the most compelling development in this field is the identification of this molecule, URAT1, as the major mediator of proximal tubule urate reabsorption in the kidney. URAT1 is a member of the organic anion transporter family. It has this multiple pass transmembrane protein structure and it functions as an anion exchanger,

more active for organic anions than for inorganic anions. It is thought that the anions in the intracellular side of the proximal tubule cells are triggering urate reabsorption by this exchange mechanism. I only conceptualize that it goes through the middle of this molecule. We are not sure if that is the case.

URAT1 is to be contrasted with another molecule, UAT, uric acid transporter, which is actually a urate anion channeler and urate here is thought to go through the middle of this membrane protein, and this membrane protein is not a member of the organic anion transport family. This is not an exchange process. It is driven electrochemically and is subject to regulation by a number of mediators, including sugars, including adenosine and including oxonic acid.

When one looks at what happens at the level of the proximal tubule in the nephron, URAT1 sits on the luminal side and promotes urate reabsorption, triggered by a number of organic anions. Lactate includes some of the ketoacids

generated by burning fat with some of the popular low carb diets, and includes metabolites of the anti-tuberculous drug pyrazinamide and basically it is inhibited at the luminal side by benzbromarone, probenecid, losartan, sulfinpyrazone and actually also high doses of salicylates. Urate reabsorption into the circulation at the basolateral membrane is mediated probably by UAT and by another member of the organic anion transporter family.

It is important to remember that urate movement at the proximal tubule is bidirectional so there is a secretory pathway that probably has a maximal capacity of about a quarter of that of the reabsorption capacity in the proximal tubule. There are potential mediators of this process that are identified and we believe that UAT and a sodium-dependent phosphate co-transporter and another member of the OAT family carry out this process.

So, we have a situation where the organic anion transporter family, also known as the SLC-22 family, is highly regulated, and gender is one of

the factors that regulates expression of these proteins, as well as aging, development, hypertension, hyperuricemia itself, renal failure and the effects of certain drugs. So, we have a situation where we know that almost all the serum urate is filtered; that there is bidirectional urate movement at the proximal tubule, predominantly reabsorption but also secretion; and that reabsorption is finely tuned, probably by other OAT family members but also possibly by the sodium hydrogen ion anti-porter whose activity goes up in metabolic syndrome and normally only 10 percent of the filter load is increased.

But there has been a very important development pharmacogenomically in that subjects who have defective URAT1 expression--and these subjects have a disorder that is known as idiopathic familial renal hypouricemia and now it is no longer idiopathic because it has been linked to URAT1 mutations--these subjects do not significantly alter their uric clearance if they are given probenecid, pyrazinamide or

benzbromarone. So, we realize that URAT1 is an interesting pharmacogenomic issue and also a very compelling specific drug target.

The problem though with uricosurics is that the effectiveness of altered uricosurics is limited by chronic renal insufficiency. There is an element of uric over-production in 10-25 percent of patients with primary gout and that imparts urolithiasis risk, and there are other side effects and drug interactions at play.

So, there has been a lot of interest in the potential therapeutic role of uricase for patients with gout. Uricase oxidizes uric acid to a much more soluble compound, lantoin, generating hydrogen peroxide. Basically, it is a critical means in lower species to convert the relatively insoluble uric acid to highly soluble lantoin. If you look at the serum urate of a normal mouse, it is 1 mg percent but the uricase knockout mouse, generated by Kowski and his coworkers, developed serum uric levels of 10 mg percent and get uricosuric tubulopathy and will die unless they are

given a xanthine oxidase inhibitor.

So, uricase gene silencing in human beings renders human uric balance quite precarious because urate is insoluble in vitro at about 7 mg percent. So, recombinant uricase is actually FDA approved for short-term, single course use in pediatric hematologic malignancies, and produces profound acute urate lowering, typically 10-15 mg/dl down to 1-2 mg/dl, and has been effective in preliminary studies short-term in gout patients. It has the potential for accelerated tophus dissolution in terms of months.

The issues with recombinant uricase are that it is highly immunogenic, being transcriptionally silent in human beings, which limits both its safety and efficacy, and some of the side effects seen over years of use of non-recombinant uricase in Europe and recombinant uricase worldwide have been respiratory distress and anaphylaxis. Then the hydrogen peroxide generation limits safety in specific patients. There are concerns about cell transformation in

vitro because of the hydrogen peroxide generation, and in vivo hemolysis in patients with G6PD deficiency and hemoglobinemia have been reported.

In patients with tumor lysis syndrome, obviously a complicated thing to treat, neutropenia, sepsis, hypocalcemia and hypophosphatemia all have been reported in a few percent of patients treated with rasburicase for tumor lysis syndrome and alkalinization of the urine can promote these electrolyte disturbance, it appears, in association with uricase use. The drug is potentially lethal and is not orally bioavailable, and clearly clinical trials of less immunogenic forms are of interest and are in progress for gout.

I would propose that the therapeutic niche for concomitant uricase in gout to be limited term treatment, with a long-lasting recombinant uricase preparation of low antigenicity for the reduction of macroscopic destructive tophus burden in highly selected patients.

What about asymptomatic hyperuricemia in

vascular disease? This topic has received a lot of press of late and it is important because there are many more patients with asymptomatic hyperuricemia than there are with gout. The press is from a fair amount of really good literature that tells you that serum urate levels correlate with untreated blood pressure in children between the age of 6-18, and that hyperuricemia is a very powerful predictor of atherosclerosis and arterial occlusive events and adverse outcome in primary vascular diseases.

A striking example is a 12-fold higher cardiac death rate in stroke survivors at 5 years, adjusted for renal function in those who are hyperuricemic. And, I am not saying that we should ignore such data. And, serum urate may be--may be and independent risk factor for atherosclerosis and certain atherosclerotic vaso-occlusive complications.

Basically, there is a large amount of recent data that I have used, quite controversial, that suggests direct linkage of hyperuricemia to vascular smooth muscle dysfunction, increased

sodium reabsorption, hypertension, glomerulopathy, cyclosporine nephropathy and chronic renal insufficiency itself. The question has arisen is markedly elevated normal serum urate in a human being, such as the levels of 7, 8 that we see in a human being, a beneficial or a harmful result of evolutionary human uricase gene silencing?

Basically, if we are dealing with human evolution, we realize that a key step was the evolution of hominids to more upright posture and, at about the same time uricase became silenced at the transcriptional level in higher primates. What has been done to address the issue of whether a normal serum uric acid level of approximately 6 mg percent or mildly elevated hyperuricemia, 7-8 mg percent, in a human being may directly cause vascular disease is to use a specific model where oxonic acid, a uricase inhibitor, is given to rats. The serum urate rises from approximately 1 mg percent to 2-3 mg percent.

What happens in this model, which has been developed primarily by Richard Johnson and

colleagues, is that the increased hyperuricemia that is seen in this model correlates with activation of the renin angiotensin system, more sodium resorption, higher blood pressure, and there is also some in vitro data that adding uric acid to cultured cells will induce the proliferation of these cells, induce COX-2, induce certain chemokines and induce MAP kinase activation.

What are the flaws in interpreting this model that we can bring up? One of the flaws is that oxonic acid directly inhibits the function of UAT which has an oxynate binding site. So, it has the potential to promote intracellular retention of urate and other solutes in cells of the vasculature.

Then, the other limitation is that direct uric acid infusion in healthy human adults, which has been performed by Waring et al., did not alter any hemodynamic or endothelial functions. Urate handling as well as serum urate levels may differ markedly in the rat and human and the cellular effects of soluble uric acid in vitro are subject

to artifacts because of potential micro crystallization.

Basically, what we have is a situation where uric acid in humans has good effects in that it is an antioxidant. It is 8 times more abundant in human serum than ascorbate. Human ascorbate production actually was lost in evolution in parallel with uricase. And, uric acid actually appears to protect against oxidant induced in hypoxic brain and heart injury. Again, under certain conditions uric acid may be a pro-oxidant and soluble uric acid may turn on genes. So, the good and the bad effects of hyperuricemia may depend on the nature of the host, much as it depends on the culture conditions in vitro.

Some food for thought before I talk about surrogate endpoints for a couple of minutes--gout is evolving clinically and clearly refractory gout and gout are rising. Better preventative efforts population-wide are needed, including patient education. Development of new treatments has not kept pace with medical needs. Typical asymptomatic

hyperuricemia has not been proven to directly cause renal or vascular disease, and gout and hyperuricemia are well understood in management but not well enough.

So, we have a situation in which we have uric acid, indicated by these stars, that is physiologically kept in solution below about 7 mg percent, and physiologically eliminated, and when we have imbalance in either purine production or intake or urate elimination, we get supersaturation and tissues are supersaturated. Tophi are formed.

Our goal is to either apply dietary measures, anti-oxidase inhibitors, uricosurics or uricase in some circumstances to allow these tophi to resorb. We will ultimately then see less intense and less frequent gouty arthritis and we will have less supersaturation in tissues that will promote tophus resorption.

How do we do this in somebody who is, let's say, hypersensitive to allopurinol or truly allopurinol intolerant? Our options really are limited. You know, the ideal situation is no

chronic renal insufficiency and urate under-excretion where we can apply a uricosuric.

Allopurinol desensitization is a 50/50 proposition in terms of success and oxypurinol is probably better than that, as we will hear today from what I have read. If a patient is allopurinol tolerant and has refractory gout and we are not putting them into a clinical trial, do we push allopurinol? Can we combine allopurinol with probenecid? There is very little data on these situations.

So, the issues regarding clinically meaningful and optimal surrogate endpoints for clinical trials include the synergistic role of combinations of anti-hyperuricemic therapies. The problem is that precipitation of gouty inflammation of urolithiasis are side effects of effective serum urate lowering, and allopurinol and uricosuric intolerance and failure need firm definitions. For example, too low or too high allopurinol dosing does not constitute treatment failure.

Other issues are that serum urate is going to be less informative than measuring the total

body urate pool, and I would propose that newer fluorescent labeling protocols be developed by targeted grants, I would hope, to add better measures of body urate pool. And, we need to have better simple measures of uric acid production levels and uric acid excretion levels in the kidney than what we have today.

How consistent is urate and how many times to measure has been raised as an issue. Then, there is the question of the percent drop in serum level versus the absolute drop in serum level. Do you drop to a target "sweet spot" level of, for example, 5-6 mg percent? Or, do you try to go slower or lower?

What do you do in terms of patients with chronic renal failure? I think it is important to point out that creatinine clearance is going to be a superior measure than serum creatinine to interpret results, particularly in elderly patients in these trials.

Serum urate in disease phenotype becomes an issue because of the effects of gender that I

have mentioned; the effects of diabetes itself; as well as chronic renal insufficiency and CHF; as well as all the other things patients are doing.

I bring up a few questions. One study of a calcium channel blocker compared to beta blocker for hypertension management in patients with cyclosporine use showed that the calcium channel blocker lowered serum urate by 10 percent, whereas the beta blocker lowered urate by zero. So, sometimes the way that hypertension is managed alone can have an impact on hyperuricemia depending on the clinical setting.

Then, the anti-inflammatory properties, albeit somewhat low grade for statins, also may be higher grade for PPAR gamma agonist anti-diabetic agents may have to be factored into interpretation of clinical trials with modification of gout.

Then, in terms of tophus size, we need validation of parameters for size change and manual measurement of superficial tophi, and the threshold for change by radiographic assessment, such as MRI, is really not defined, and we don't know whether to

measure both grossly uninvolved and involved joints because with the uninvolved joints, if you aspirate some of those joint fluids, you may see urate crystals and that is not really rare.

Then the issue of needing quality of life instruments and assessing the frequency and severity of gouty attacks; the length of attacks; the number of anti-inflammatories consumed--would those be useful parameters to look at? And, which shorter and longer specific times points to look at? We need instruments like an ACR-50 or a HAQ optimized for gout. The one that we are trying to play with at UCSD is a drop in serum urate in milligrams per deciliter, divided by the fraction of gouty attacks per month between 3-12 months relative to baseline, and then trying to come up with some numbers for validating that particular instrument. It is a very poor instrument but it is a start.

Then, the role of pharmacogenomics and optimal clinical trials of anti-hyperuricemic drugs--is there a role for identifying patients who

have SNPs and URAT1 and other OATs, and UAT? Is it important to identify hyperuricemia that is possibly mediated by dysregulated tissue UAT as distinct from a true increase in the body urate pool? I think, as we will see maybe 5 or 10 years from now, this will be a significant issue.

I want to think about identifying also altered pyrimidine metabolism in non-immune allopurinol toxicity as another pharmacogenomic tool. Finally, identifying subject redox stress may also help in pointing out who is more susceptible to uricase toxicity.

So, thank you for your attention.

DR. GIBOFSKY: Thank you, Dr. Terkeltaub for an excellent presentation. I would like to take a moment, if there are any specific questions from the panel for Dr. Terkeltaub before we go on. Dr. Cush?

DR. CUSH: You implied that we should be looking at tophi as a measurable outcome. Can you inform us as to the evidence that reducing tophi improves quality of life and subsequent attacks?

You were sort of talking about tophi as sort of a measurable pool or tangible measurable pool of total body urate as opposed to just going to serum uric acid levels. I mean, we would look to prevent gout by looking at attacks. Clinically we usually don't target tophi because when they show up they have so many tophi--we would like them to go away and we take that as a goal but we often don't see that in practice.

DR. TERKELTAUB: That is a good question. I think, you know, with modern imaging techniques we may be able to see in a better manner microscopic tophi in the synovium, and we will be able to better understand how to reduce the urate crystal burden at the joint level. Basically, given that the disease includes connective tissue destruction mediated by those deposits, I think that is a large issue.

The problem here is that as you decrease tophus size you may get more symptoms vis-a-vis attacks of gouty inflammation. Whether it has been studied adequately, clearly not. There have bee so

few clinical studies over the last 20 years.

DR. GIBOFSKY: Bob, you pointed out that erosions can progress even with effective lowering of serum uric acid. To what extent then ought we to be considering imaging as an outcome measure in clinical trials for any anti-gout agent?

DR. TERKELTAUB: Yes, thank you for the question. I was referring to a study by Bob Wartman and Geraldine McCarthy about 12 years ago. Basically, they looked at the first toe and they saw, with gross radiographs, that there was progression over a fairly long time period with adequate serum urate lowering and, basically I think there is a lot of room for optimizing a better trial today using more modern imaging techniques.

DR. GIBOFSKY: Dr. Bathon?

DR. BATHON: I was just remembering one of the NSAIDs, etodolac, clinical trials that caused significant lowering of uric acid. I was wondering if it could be clinically efficacious.

DR. TERKELTAUB: Several of the NSAIDs can

modulate urate excretion, not huge effects. I think they become more important to consider when you are trying to understand what the etiology of the hyperuricemia is, other than aspirin, of course, and salicylates.

DR. GIBOFSKY: Dr. Felson?

DR. FELSON: Bob, that was a wonderful comprehensive talk. If we are going to consider uric acid as a surrogate marker, it seems that we need to know a little bit more about the repeatability of measurement, the sources of variability over time of the day and from day to day. When I was in medical school I learned that there were a number of different assay techniques for uric acid and that they weren't necessarily consistent in their results. Could you start with that? Is that still true or is there some real consistency across various labs in given specimens and what levels they produce?

DR. TERKELTAUB: The standard measure right now for serum uric measurements is adopted nationwide. There used to be a uricase method that

was used in some labs and a distinct method used in other labs. In terms of the reproducibility between patients, there haven't been terrific studies done. Most of the studies have been done on a population level to construct bell curves and there haven't been terrific studies done vis-a-vis individual patients.

DR. FELSON: Does uric acid vary by time of day in a given person? It was hard to use cholesterol, for example, as an outcome measure in trials because there was a lot of variability from hour to hour and from day to day in people; blood pressure similarly. That is one of the reasons why we get multiple measures of blood pressure to make a diagnosis. Is there a similar variability in uric acid?

DR. TERKELTAUB: Not to my knowledge.

DR. FELSON: But it sounds like it hasn't been well studied.

DR. TERKELTAUB: It hasn't been well studied since I have been a rheumatologist. That is the problem.

DR. GIBOFSKY: Any other questions? Dr. Hoffman?

DR. HOFFMAN: The comments about the Wartman study and continuing erosive changes after normalization of uric acid, is that in part because all gout is really micro tophaceous, it is the product of so many years of laying down sodium urate and normalization of serum uric acid is really the curve towards gradual resorption of tophi. So, when we look at clinical endpoints using imaging, it really wouldn't be so meaningful to look at radiographic endpoints for something less than perhaps a year after the accrual of increasing micro tophi within the joint was aborted and resorption had meaningfully progressed.

DR. TERKELTAUB: Yes, I think we believe that serum urate is the large tip of a large iceberg, and I would challenge clinical investigators to look at more sensitive methods of imaging the synovium of joints to look at small tophi and to try to calculate the size changes.

DR. GIBOFSKY: Dr. Hochberg?

DR. HOCHBERG: If we are going to look at the recurrence of acute attacks of gout, let's say, in someone who has had prior gout and has hyperuricemia to assess the efficacy of a long-term therapy, would one do that in a patient who would be entered into a trial who is on background colchicine therapy, which is at least accepted therapy to reduce the risk of recurrence of acute attacks, and see whether an agent in addition to colchicine was better than placebo in addition to colchicine? Or, would you consider doing this instead of colchicine?

DR. TERKELTAUB: I would consider doing it with colchicine pretty much. I think that basically the most common side effect we see with allopurinol, for example, is precipitation of acute gouty attacks. The data are not great for this. I mean, we know that the gouty attacks are usually precipitated most frequently in the first couple of months of allopurinol treatment, but with uricosuric treatment, which is titrated by everybody out there more steadily, there is are few

gouty attacks precipitated. Has that been studied in a really good quantitative clinical trial? No, but I think people who are experienced clinicians know that is probably the truth. I don't think that withdrawal of colchicine would be a good thing in terms of constructing clinical trials.

DR. GIBOFSKY: Thank you, Dr. Terkeltaub. I think at this point we will move to the next portion of the program which is a presentation by Cardiome Pharma, Inc. We will ask Dr. Moore, the Executive Vice President for Clinical Development and Regulatory Affairs of Cardiome Pharma Corp. to introduce the program and the speakers for that portion. Dr. Moore?

Cardiome Pharma, Inc.

Introduction

DR. MOORE: Well, good morning, ladies and gentlemen. We are here to talk about oxypurinol for gout. I am Alan Moore and I am the Executive VP for Clinical Development and Regulatory Affairs of Cardiome Pharma.

My role here basically is three-fold. I

am going to give you a very brief introduction to Cardiome Pharma. Then I want to talk about the regulatory history of oxypurinol because it is really quite extensive, as I am sure you know, and finally talk about the concepts of the agenda and the agenda itself.

First of all, let me start with Cardiome Pharma. We are an R&D company that is based in Vancouver, Canada. We focus on cardiovascular drug development. As I am sure you are aware, there is a large component of anti-inflammatory in cardiovascular so, consequently, we have frequent interactions with both FDA's cardiorenal and anti-inflammatory drug divisions as well.

Let me talk about oxypurinol regulatory history. In 1966 Burroughs Wellcome filed an IND for the compassionate use program for oxypurinol. The reason was that in 1963 Burroughs Wellcome had marketed allopurinol and had quickly observed allopurinol-intolerant patients. Consequently, in '66 this compassionate use program started, which was designed to provide oxypurinol for allopurinol-

intolerant patients.

In 1996 ILEX acquired the IND for the use of oxypurinol, and in 1998 the drug received an orphan drug designation. As you will hear later, this is a very small population of patients that we are talking about.

In 1999 the pivotal study OXPL213 was initiated, and you will hear a lot more about that later on this morning. In 2002, Cardiome Pharma acquired the IND for this drug and we filed the NDA on December 23 of 2003 which is, of course, part of the reason that we are here today.

Dr. Witter had talked about Subpart H and, as I said, the way the majority of patients who received this drug was by compassionate use. So, let me talk about the benefits of Subpart H approval, which we have been talking about extensively today with the FDA, versus the current compassionate use program.

First of all, Subpart H approval provides patient education; provides restrictive patient enrollment criteria; provides a patient registry;

provides physician education and training; provides collection of safety data and fewer patients lost to follow-up. Of course, the converse is true of the compassionate use program.

So, the proposed indication that we are looking for oxypurinol is--let me read it, oxypurinol is indicated to treat hyperuricemia in patients with symptomatic gout who are intolerant to allopurinol and have failed either rechallenge or desensitization with allopurinol. To be clear then, this is a doubly intolerant patient population, and what we are talking about here are people who have not just failed allopurinol once but have also failed twice because they failed either a rechallenge or a desensitization, again, making the population that much smaller than what we have been talking about before.

Now, what does oxypurinol provide for these allopurinol-intolerant gout patients? Well, it addresses an important unmet medical need. We have already heard from Dr. Terkeltaub that allopurinol-intolerant patients have very limited

options and, clearly, oxypurinol provides an option. Secondly, oxypurinol has demonstrated good clinical efficacy, and we will talk about that later on in the presentation. Next, it is well tolerated in the majority of allopurinol-intolerant patients. Not to emphasize the point here, but the patients we are talking about are 100 percent intolerant to allopurinol; they simply cannot take it, whereas, 70 percent of them can take oxypurinol, and we will talk about that later as well. Finally, as Dr. Witter mentioned, under Subpart H there will be additional safety and efficacy issues addressed, first by the Subpart H risk management program but, secondly, by a Phase 4 study, that we will also talk about later in some detail, that is currently under way in our hands that talks about clinical outcome and compares that with serum uric acid as well.

So, let me introduce the speakers and topics for today. First of all, with have Dr. Ralph Snyderman, from Duke University, who will be talking about gout as a serious progressive

disease. Secondly, we will have Dr. Garth Dickinson, from the University of Ottawa, who will be talking about oxypurinol efficacy and safety. Thirdly, we have Dr. Robert Makuch, from Yale University, who will be talking about OXPL213 analysis, and this is our key pivotal study. Finally, Dr. Leonard Calabrese, from the Cleveland Clinic, will be talking about his clinical experience and post-approval issues with oxypurinol. So, thank you for your attention. Dr. Snyderman?

Gout: a Serious Progressive Disease

DR. SNYDERMAN: Thank you, Alan. I would like to thank the FDA and the Arthritis Advisory Committee for giving us the option to talk but, more importantly, for recognizing an important serious, progressive metabolic disease which, as we have heard from Dr. Terkeltaub--one of the best presentations I have heard in a long time--this is a problem that is not only with us, it is going to be increasing as we go ahead, and it is an important clinical problem.

Gout is probably one of the best described and understood and characterized diseases virtually in all the history of medicine, having been written about by Hippocrates and his colleagues; being discussed by Galain with a description of a tophus; Garret, in 1844, beginning the revolution in medical understanding of the metabolic basis of disease; the development of uricosuric agents in 1950; and the development of allopurinol in the very early '60s.

Now, given the fact that gout is a serious metabolic disease for which there are a number of treatments, I also feel it has been badly under-recognized, the degree of the clinical problem that it is. As I was hearing Dr. Terkeltaub talking, it is almost the Rodney Dangerfield of rheumatology diseases. It doesn't seem to get the respect that it deserves.

I actually started at Duke in the rheumatology division at the time that we had Jim Weingarten, Bill Kelly, Ed Holmes, Wayne Rundells who was in the hematology division, and Durham, as

many of you know, was a hotbed of moonshine, white whiskey, and we had an incredible prevalence of gout and it was very well studied.

Very recently, on an NPR show, public radio in Durham, from the People's Pharmacy I heard a physician say that gout was no longer a medical problem, that it was so easily treated physicians don't even think about it anymore. Just having completed rounds at Duke doing my rheumatology turn, I can tell you that this is a very prevalent disease. Just seeing the patients that we are seeing at Duke, I would agree with Dr. Terkeltaub, not only is it common, not only is it prevalent but the patients are much more complicated and usually are admitted not because of their gout but because of other serious diseases, but what is bothering them the most, even though they may be dying from something else, is their problem with chronic tophaceous gout.

So, gout is a serious metabolic disease. In its untreated form it is chronic, progressive and debilitating. It is the most common form of

inflammatory arthritis in men over 40, and we are seeing it more and more in women. Many patients with gout have renal insufficiency, with primary or secondary but we suspect a substantial amount is primary. We have also heard, and there is very good epidemiological data, both from the Rochester studies and in Taiwan, that gout is increasing dramatically over the last few decades. It is occurring at a much earlier age. It is increasing in frequency even independent of other medications--primary gout is increasing in frequency and it is increasing in women. So, we need to deal with it. This clearly is a problem.

The stages of gout are well described. The first attack is usually following substantial periods of hyperuricemia. I think the discussion of whether or not there are developments of micro tophi in certain joints, such as the first MTP, is a very interesting question but we certainly know from direct experiments that one does not need a micro tophus, given the elegant studies of Dan McCarthy and P. Phelps injecting monosodium urate

crystals directly in their joint and getting a very hardy gouty attack. So, I think that is an interesting question but, nonetheless, acute recurring gout followed in some by inter-critical period and then chronic tophaceous gout. What differentiates these individuals is certainly a matter of great interest.

I think one of the reasons gout has been to some degree not given the respect that it truly deserves is the fact that it has been associated with conditions that people can bring on themselves, at least seemingly so. This has been called the disease of kings. I was interested to hear that white wine doesn't increase gouty attacks but maybe port wine does and individuals eating sweetbreads and various other things. So, this was called the disease of kings and many cartoons show the obese individual, obviously wealthy, being carried about by others with a swollen big toe.

But that is not the story of gout as we are seeing it. We are seeing it as a debilitating disease that causes a great deal of joint

destruction and the tophi, while difficult to remove, what I would say is that tophi themselves are debilitating in individuals with large tophi. There is a lot of weight and bulk to carry around and many people suffer from this.

As any rheumatologist knows, the way we used to challenge ourselves sometimes at rounds is where have you not seen a tophus? Tophi could develop virtually anywhere and they certainly develop in the kidney and many people with prolonged hyperuricemia develop urate nephropathy. Pathogenesis has already been described elegantly. Again, this is a disease in which we know so much and, yet, there are things that we still don't know. Whether the monosodium urate crystal provides a surface for complement activation or other mechanisms of inflammation, nonetheless, it is very pro-inflammatory in most individuals.

The management of gout has been very well described. I will just say briefly that we are often focused on treating the acute gouty attack, whether it is monoarticular or oligo- or

polyarticular. But in individuals in Duke Hospital this is sometimes the greatest problem by far that a patient is facing, no matter what their other disease is.

We are virtually never able to use colchicine. As much as I have used it as a rheumatologist, I can tell you when somebody is in the hospital there is always a good reason that you cannot use colchicine. NSAIDs which work extremely well also. It seems as though most of the patients that we have, have a creatinine that is higher than what we would like to see in somebody using Indocin or some other nonsteroidal. Corticosteroids--at least I see it all the time with the house staff and it amazes me sometimes that the first-line drug of choice seems to be the use of corticosteroids, whether intra-articular or systemic.

The chronic treatment of gout to actually affect the metabolic cause for development of monosodium urate crystals is, as we heard, primarily uricosuric agents, xanthine oxidase inhibitors, uricase still being looked upon

experimentally, with the most common utilization being allopurinol. I remember quite well when the compassionate clearance became available for oxypurinol, and I can tell you that for physicians having to do this is burdensome, very hard to develop follow-up and very rarely used even though many clinicians would want to use oxypurinol, in my opinion.

So, the therapeutic goals in gout--we need to decrease the frequency of attacks, the severity of attacks but what we really want to do is decrease the continued deposition of monosodium urate crystals; decrease the frequency of gouty attacks, tophi, urate nephropathies and renal colic, and there are a number of different forms of renal diseases associated with gout.

The major point I want to make, other than that gout is under-appreciated as a national problem which is going to be getting worse and it affects a segment of the population that seem to have the least options available to them. So, I believe it is a matter of justice as well to give

this problem the attention it deserves.

The figure I have is 2.5 million. Dr. Terkeltaub had 3-5 million. Clearly, this is a large number of people. As best as we can tell, roughly 1 million prescriptions of allopurinol are made each year. There are up to 40,000 individuals who, for one reason or another, cannot take allopurinol. The data that will be presented by others today is that within this population there are going to be, let's say, up to 14,000 individuals whose condition could be satisfactorily treated with oxypurinol. That is the argument that will be made by the people at Cardiome.

I would just like to put this a bit into perspective. If we look at the individuals who then potentially could be treated effectively with oxypurinol, we have allopurinol-intolerant gout patients that have already failed desensitization and are likely to be affected well by oxypurinol, you are talking about a serious disease. We think an awful lot about cystic fibrosis, as we should, hemophilia, Gaucher's and others. I applaud the

FDA and the Arthritis Advisory Committee for focusing specifically on those unfortunate individuals that have chronic gout that have no other option open to them. Thank you very much.

The next speaker is Dr. Garth Dickinson, from the University of Ottawa, who is going to talk about oxypurinol efficacy and safety.

Oxypurinol Efficacy and Safety

DR. DICKINSON: Thank you, Dr. Snyderman and good morning, everyone.

In discussing the efficacy and safety of oxypurinol I would like to focus on two main trials. The first is the pivotal trial OXPL213 and the second is the compassionate use program which is called CUP3362-01. OXPL213 was an open-label, single-arm, multicenter trial that enrolled 79 patients. The trial duration was 14 weeks. Everyone enrolled in the trial had mild to moderate allopurinol intolerance. Everyone enrolled in the trial had relatively normal renal function. Their creatinine had to be less than 2.

The primary efficacy endpoint for the

trial was a serum uric acid reduction of 2 mg/dl. Oxypurinol was dosed in a graded fashion, starting with 100 mg per day for the first week, 200 mg per day for the second, 300 mg per day for the third week. So, gradual titration in dose. Once a reduction of 2 mg/dl was achieved in serum uric acid there was no further dose escalation.

What were the results? You can see that the patients started off with a mean serum uric acid of 10.11 so they had significant hyperuricemia and they were all symptomatic patients. In the efficacy intent-to-treat population, as defined by the protocol, of 77 individuals the mean reduction was 1.90. This was just short of the primary efficacy endpoint of 2 mg/dl. However, this reduction was highly statistically significant compared outcome to the baseline number, at a level of p less than 0.0001. In the completer population, the 54 individuals who were able to complete the 14-week trial, the reduction in serum uric acid was naturally higher. It was 2.32 mg/dl.

In addition, we looked at perhaps a more

clinically relevant endpoint, and that was what was the number of patients whose serum uric acid actually fell into the normal range, and we found that in the total efficacy intent-to-treat population 38 percent dropped into the normal range. In the population that completed the trial, 50 percent of these individuals had their serum uric acid reduced into the normal range.

The compassionate use program is not a clinical trial. It started in 1966 as a result of a need for patients who could not tolerate allopurinol. Since that time there have been 533 patients enrolled in that trial. And, 533 patients represents probably over 5 percent of the allopurinol-intolerant population that this drug is intended for so this represents a large component of the allopurinol-intolerant patient population.

This was a real-world study and 38 percent of our patients had renal failure as defined by a creatinine of 2 or greater. Many of these patients are transplant patients. The average dose that the patients took at 1 year was 372 mg and there was a

fairly wide dose range, from 100-1800 mg per day. One patient in particular took 1600 mg of oxypurinol daily for 8 years without any difficulties whatsoever.

The problem with adverse reactions with oxypurinol tends to be more idiosyncratic rather than dose related. The average duration of treatment with oxypurinol is 3.2 years, with 22 years being the maximum that any one individual has been on the drug, and there are currently 162 patients taking oxypurinol in this compassionate use program and in the one that followed the 213 trial.

Looking at longer-term serum uric acid endpoints, you see that at 1 year in both the extension to the 213 trial--these were patients who were able to continue oxypurinol treatment after completing the 213 trial--and those in the compassionate use program, their serum uric acid fell by about 2.9 mg/dl. This compares to about 3 mg/dl which occurs in patients who are given long-term allopurinol therapy at 300 mg per day, again,

a highly statistically significant reduction.

Gout flares have been referred to already a few times this morning, and they are a problem when you are trying to measure the effectiveness of any particular uric acid lowering therapy. In the 213 trial we had 24 gout flares experienced by 12 patients. So, our rate of flares was about 16 percent, which compares very closely to what is experienced with allopurinol, the rate being quoted as somewhere between 10-24 percent. So, treatment with oxypurinol seems to mobilize uric acid and may be associated with gout flares, just as is the case with allopurinol.

In concluding about the efficacy of oxypurinol, there is no question that oxypurinol is effective in reducing serum uric acid in allopurinol-intolerant patients. The magnitude of the serum uric acid reductions are quite comparable to those seen with allopurinol.

Let's move on now to safety. In discussing safety I will be speaking again about two trials, OXPL213 and the compassionate use

program. The safety issues relate primarily to the 30 percent of patients who cannot take oxypurinol, 100 percent of these patients cannot take allopurinol. They are all allopurinol-intolerant. Seventy percent can tolerate oxypurinol but 30 percent can't.

When you look at the adverse events that occurred in trial 213, if you look over to the column on the right side you will see that of the oxypurinol-related events there were 30 events considered to be related to oxypurinol and 21 of these resulted in discontinuation of the drug. There were no serious adverse events due to oxypurinol. There was 1 death in the trial unrelated--due to cancer of the pancreas. There were no life-threatening adverse events due to oxypurinol. There were 3 severe adverse events. Two of these were severe skin rashes and one was a significant elevation in liver function tests.

When we look at the adverse events that prompted oxypurinol discontinuation, you can see a recurring word here, dermatologic, dermatologic.

The vast majority of adverse events with oxypurinol are skin rash, just as is seen with allopurinol.

The other thing that you see here is that of these 21 patients that had to stop oxypurinol in the trial, 19 of them had exactly the same reaction to oxypurinol as they had with allopurinol. So, in any one individual it is quite predictable what kind of adverse event you are likely to come up with.

The final point here is that it is not just skin rashes. There are other things that can occur, there are other adverse events. These typically are clinically silent so it could be myelosuppression, thrombocytopenia or it could be elevation in liver function tests. So, it is important that patients who are started on oxypurinol be carefully monitored both clinically and by laboratory evaluation.

In terms of the adverse events that caused discontinuation of oxypurinol, they occurred early and 71 percent of them occurred in the first week, while they are on 100 mg per day. They are

predictable. In any individual, if they are going to have an adverse event, there is a 90 percent chance it will be the same event they had with allopurinol. So, if they had a rash you watch for a rash. If they had liver function problems on allopurinol you watch for liver function problems. Ninety percent of them were mild or moderate and all of the adverse events were entirely reversible. Remember, in this trial we did not enroll anybody who had had a severe reaction to allopurinol. These are mild or moderate allopurinol reactions.

When we look at the compassionate use program, we see that there are many more serious adverse events. This is an elderly population with multiple co-morbidities. Importantly though, look again over at the column on your right side. Since 1966, investigators using oxypurinol have never reported a serious adverse event related to oxypurinol. That is a pretty astounding safety record. There have been no life-threatening adverse events reported either. Over 1500 years of patient dosing are included here.

Let's turn now and look at hepatic adverse events. In the 213 trial 6 patients had hepatic adverse events to allopurinol who were enrolled in the trial. Of these, 2 had the same type of mild liver function abnormalities to oxypurinol. In the compassionate use program we identified 20 patients who had had liver function abnormalities on allopurinol. When they took oxypurinol, 6 of them again had the same type of liver function abnormalities and had to be withdrawn. The consistency here is that still about 33 percent of individuals were having the same type of reactions; 30 percent of individuals who can't take allopurinol also can't take oxypurinol.

When we look at this from a slightly different angle and we look at all the hepatic adverse events that occurred in the 213 trial or in the years of the patients who continued on oxypurinol, we found 6 episodes of hepatic dysfunction. Two of these were considered to be probably related to oxypurinol and in both those instances the patient had experienced abnormal

liver functions while taking allopurinol. So, these patients dropped out. One dropped out early in the trial and one completed the trial but dropped out after the end of the trial and didn't continue on. All of the other hepatic abnormalities that occurred in these patients were considered unrelated to oxypurinol therapy by the principal investigators. In three of the four cases oxypurinol was continued for prolonged periods and no further adverse events occurred.

So, for safety conclusions for oxypurinol, 70 percent of patients who are allopurinol-intolerant can tolerate oxypurinol. The adverse events that do occur with oxypurinol occur early. They are predictable. They are reversible. There is risk of hepatic toxicity and it is important that any patient who is started on oxypurinol be followed and managed in an appropriately structured clinical environment. There has been no evidence of significant harm with oxypurinol. There have been no drug-related serious adverse events reported with oxypurinol. So, in this population

who are 100 percent allopurinol-intolerant, in this population oxypurinol is much safer than allopurinol.

Thank you. I would like to now introduce Robert Makuch, from Yale University, who will look at a statistical analysis of the 213 study. Thank you.

OXPL213 Analysis

DR. MAKUCH: Good morning. I am here to discuss the analysis of the pivotal trial for oxypurinol, OXPL213. I would like to take a step back just for a minute and summarize my recent involvement in this effort. This included my review of numerous documents, including the pivotal study data, the study protocol, the analysis plan and related documents. Based on my independent assessment, there were certain limitations to the study that included inconsistencies or incompleteness of various efficacy endpoint definitions in the analyses.

This led me to propose, prior to looking at any of the data, alternative endpoints and

analytic methods. What I would like to do this morning is review for you these alternatives with two goals in mind. The first is to provide you with additional information that may be useful in your discussion today regarding guidelines for chronic gout studies. Secondly, to help you understand more fully the results from this pivotal trial.

To review briefly, for the primary efficacy objective for this pivotal study the goal was to demonstrate the efficacy of oxypurinol in lowering serum uric acid by at least 2 mg/dl after 14 weeks of its administration to symptomatic hyperuricemic patients who have developed an intolerance to allopurinol. This primary objective was operationalized by defining the primary efficacy endpoint as follows: One would consider the mean of the 3 baseline assessments and from that, for each subject, subtract the mean of the assessments made at weeks 12, 13 and 14, or for those subjects who did not have values at these time points we would then consider the last

available assessment that would then be used for the analysis.

This endpoint definition, as you can see, is somewhat inconsistent in the sense that we used the average of 3 values for patients at their treatment termination for those who did make it to the end of the study and we only used one value for those who discontinued early. We will return to this issue later.

I would like to just review for you briefly the patients that will comprise the basis for my analysis. There were initially 79 subjects enrolled who took at least 1 dose. On the other hand, there were 2 subjects for whom there were no post-baseline serum uric acid values available. They were discontinued for reasons unrelated to study drug and so, per the protocol, the ITT or intent-to-treat efficacy population then becomes 77 subjects. Of the 77 subjects, of those who completed 14 weeks of they, we had a total of 54 subjects. The remainder discontinued early with 23 such subjects meeting that particular criterion.

Of those 23, there were 8, in fact, who had no post-baseline serum uric acid values.

So, my analyses then will focus on two groups. One will be the original ITT per protocol population of 77 subjects. The other will be the 77 minus the 8 subjects who did not have post-baseline, or 69 subjects then who had at least 1 post-baseline SUA value. The reason, in part, is that this often is used as the intent-to-treat population in other studies.

To focus just for a minute on the 8 subjects who did not have a post-baseline SUA who were unable to tolerate oxypurinol, we note in the analysis that they were originally assigned a SUA change value of zero. Clearly, this would compromise the ability to detect a SUA reduction of greater than or equal to 2.0 since we have 8 subjects of the 77 having a value imputed of zero. This is not an optimal statistical approach for two reasons. One, for these 8 patients we are imputing a value of zero. More generally though, the change value doesn't take into account all the data that

were collected on these patients. In fact, the data were collected on these patients not only at baseline and at weeks 12, 13 and 14 but, in addition, we had data collected as well at week 6 and at week 9. So, in fact, we have a good set of information available on all subjects as they proceeded through their entire treatment course.

What I would like to then do is to just briefly describe some of the alternative endpoints that I considered prior to looking at the data, as well as an additional analysis that I thought would be meaningful in terms of getting a fuller appreciation for these data. The alternative endpoints included the proportion reverting to a normal SUA level, and you have already heard Dr. Dickinson present the results for that. The second alternative endpoint is to consider the baseline average for all the subjects but just minus the last value. So, what we are then doing here is applying a consistent definition to all the subjects. Namely, we are going to take the last value for all the subjects as opposed to taking

several values for some subjects and taking just the last value for other subjects, as was done in the original protocol and the original analysis plan.

Secondly, I will also present the regression analysis which takes into account all the data. The reason I find this to be very useful and perhaps the preferred method is that it does use all the data in the full intent-to-treat population of 77 subjects and, secondly, we do not impute any data.

To summarize the results of this analysis, again, we have the 77 intent-to-treat for the population and here we are looking at the change from average baseline to just the last value. Therefore, upon the reduction in the SUA we get a slightly different result than what was presented to you earlier because it was based on somewhat different data in terms of some patients--3 values for some patients and other patients just 1 value. Here we are taking just the last value for all the subjects and then you do get a reduction of 1.95

with a confidence interval as seen and, again, a highly statistically significant reduction in the SUA values between baseline and week 24.

The second analysis includes all those for whom we had at least 1 post-baseline SUA value, the 69 subjects. For that group we then get a reduction in the SUA value of 2.12, again with the corresponding confidence interval as you can see, again a highly statistically significant reduction in the SUA values over time associated with oxypurinol. Clearly, the mean value then does exceed 2.0.

The best way I think to look at these data is with a regression analysis since it uses all the data for all the patients, with no data imputation. At Yale I guess we call this the spaghetti plot. It looks sort of like you threw spaghetti on the graph but essentially this is all the data that we have and, as you can see, it does point out the information that we have at week 6, week 9, 12, 13 and 14 which are the values at which measurements were taken, as well as all the information for all

the subjects.

The dark line is the regression line that we will describe next. One point though is to note that there is a market decline between baseline and week 6 and then that levels out from week 6 out to week 14. This is actually quite consistent with the dose escalation scheme that was used in the study, in which the doses were increased up until the week 6 period and then modifications were made for those who did not achieve a 2.0 mg/dl reduction. So, in some sense, this trial was dosed in a way that was titrated towards a reduction of 2.0, which I think has to be considered when looking at the results at the end of the study which, again, are around 2.0.

So, in the regression analysis, just to describe it, we did a linear regression with both linear and quadratic terms. When one applies it to the data that we saw in the previous slide, at week 14 there is a mean drop of 2.37 mg/dl in the serum uric acid level. Moreover, the 95 percent confidence limit ranges from the low of 2.06 to

2.67. So, not only is the average drop in excess of 2.0 but also the lower 95 percent confidence limit for this mean also exceeds 2.0.

So, the conclusions are that using and considering alternate endpoint analyses, whether we look at the N of 77, which is the full intent-to-treat population in which we have, for the last value analysis, a value of 1.95 being the mean drop, or the 69 subjects, all of whom have at least 1 post-baseline SUA value--again, an intent-to-treat population often defined in protocols, or whether we look at the regression analysis which uses all 77 full intent-to-treat population per the protocol and in which we have a significant drop and you saw the confidence interval earlier which, again, is in excess of 2.0, clearly all the analyses show a highly statistically significant reduction in the serum uric acid values.

In my opinion, future studies then should consider at least regression analysis since they do look at all the data for all patients with no data imputation. Admittedly,; the current study, as

designed and analyzed originally, did not meet the primary endpoint of a 2.0 or greater decrease. However, these results should be considered in the context of these alternative analyses, the dosing schedule used in this particular study--you will hear more about this, and you have heard a little bit already, that a restrictive Subpart H risk management program is being proposed, and that a Phase 4 study has been designed to address limitations of this current pivotal study.

Thank you. The next speaker will be Dr. Calabrese who will discuss clinical experience and post-approval issues.

Unmet Medical Need/Clinical Experience and Post-Approval Issues

DR. CALABRESE: Good morning, Mr. Chairman, members of the committee and members of the FDA and guests, it is my charge to talk about some practical clinical issues with oxypurinol. I would like to start by saying that Dr. Terkeltaub and Dr. Snyderman have already elegantly described gout as a disease not only of antiquity but a

disease where there is considerable morbidity and mortality. I like to tell house staff and students that for the vast majority of cases of gout, it is a very, very treatable disease, eminently treatable, but for a small percentage of patients, and a percentage that I think is increasing, as previously described, with multiple co-morbidities, particularly those with drug intolerance given the few drugs that we have available, it is really a complex situation.

One of the more particularly vexing problems for clinicians is when we face patients who are allopurinol-intolerant, particularly those with high urate loads, chronic tophaceous gout which is so often complicated by mild renal insufficiency, leaving only two pathways to deal with these patients. One is to pursue allopurinol. One could rechallenge. One could subject them to desensitization technique, which is complex and laborious, not universally available and one that is flawed given the sizeable number of patients who will fail desensitization. Oxypurinol for this

population is the only option, and I will talk a little bit about the experience with it, which will actually treat the underlying metabolic disorder.

Otherwise, we are relegated to a treatment path if symptomatic and supportive care. Yes, we can reduce the number of gouty attacks. We can reduce morbidity. We do nothing to affect the metabolic problem that belies the disorder and to forestall end-organ damage from this infiltrative, destructive and inflammatory disease.

Now, at the Cleveland Clinic we have a sizeable experience with oxypurinol. I reviewed this in anticipation of this meeting and I was surprised to find out that my experience with this drug goes back over 20 years. It seems just like the other day that I started putting patients on this. Sixteen patients, including 13 in the compassionate use and 3 in the pivotal trial, and consistent with the data that was just presented, of these patients, 2 were intolerant and had mild cutaneous reactions and were withdrawn. The remaining patients were treated from approximately

a month to over 10 years.

I would just like to share with you three vignettes of patients that I currently have on long-term oxypurinol, just to give you a flavor of how I have come to understand this drug and utilize it in my armamentarium of treating this disease.

One is a patient I have treated for a number of years who had increasingly frequent gouty attacks, intolerant to allopurinol, mild renal insufficiency, and he has been totally controlled on oxypurinol and has been gout-free for a number of years.

The second patient I think is familiar to all of the rheumatologists in this room. This is an elderly woman who had a successful renal transplant. She also has draining tophi. She is highly allopurinol intolerant, and she is on long-term calcineurin antagonist with cyclosporine that maintains her creatinine in the mid-2s. I have had her on oxy at a dose of about 300-400 mg a day and she has been gout-free and has been experiencing regression of her tophi over the past few years.

The final case is really instructive to me and has meant a lot to me, and I want to share this vignette in just a slight amount of detail. This is a patient JH. He is a very robust, well-traveled civil engineer who, in the early '90s, became increasingly debilitated by gouty attacks, increasing in frequency, tophaceous, and he had reached a point where he had enlarging tophi, including one on his foot, very similar to the one Dr. Terkeltaub showed that graphic picture of. It involved the toe, complexly involved the web space, had eroded through the skin, was chronically draining, was a site of recurrent cellulitis.

He was treated by a fine internist in Cleveland who knew that this guy was an allopurinol candidate and needed allopurinol, and he treated him and he rashed. He also has a creatinine of about 2.5. Knowing that he had no other options, he retreated him and he rashed again. Knowing the desperation of this individual with this progressive course, he actually instituted low dose graded desensitization, and with each gradation of

dose Mr. JH had progressively more severe rashes and intolerance. He ultimately was referred to me.

I entered him on compassionate use and escalated his oxy up to 400 mg a day under the cover of colchicine. I can tell you the experience summarily. One, this man has never had another attack of gout in over a decade. Number two, his tophi have either regressed; some have disappeared but the largest ones are still there but totally healed over. There is no doubt--you don't need a statistical instrument to assess his quality of life.

Now, having seen this patient every three months, giving him this drug over the years, we have become friends and I talked to him about coming to this hearing today. He kind of sheepishly told me, he said, I want you to tell them. He said because when I first came to see you--you know, he had been engineering at all these large dam projects, a really kind of a manly guy--he said, I was depressed; I was nearly suicidal--because he was looking at a transmetatarsal

amputation. It is a vignette but meaningful to me.

So, based upon this experience and utilizing this drug with some comfort, you know, I am trying to make a case that I think that risk/benefit is favorable but there are still outstanding issues with this drug clearly. One, it would be highly desirable to obtain clinical data from a study, a meaningful clinical endpoint. And, should it reach regulatory approval, I would want to see a system in place that limits access to this to appropriate patients, used in a wise manner by knowledgeable physicians.

I believe there are two programs here, including this Phase 4 trial that was alluded to and the risk management program that I would just like to briefly describe in closing.

The Phase 4 protocol, which is just getting under way, was crafted with consultation with the FDA, and this is a 2-year randomized, placebo-controlled trial of oxy in 240 patients. The primary endpoint of this study will be reduction in gouty attacks. Patients have to have

at least 6 attacks during a calendar year coming into the study. It will also assess reduction in tophi. There are quality of life measures and serum uric acid reduction.

I think all of us would agree that if this study were completed it would provide meaningful information about some issues that we just don't have at the present time, correlating clinical outcomes to serum uric acid.

In addition, the risk management program I think is critical. What has been proposed is that this drug would be distributed by a centralized pharmacy and there would be a physician education program that would ensure a knowledge base before being able to write for this. This would be web-based. There would also be a resource of patients to help them understand their disease and its treatment.

Once a patient has met the criteria for going into the study, a form would be electronically transmitted and this would be verified before dispensing drug. I think most

importantly, this type of risk management system would allow the tracking of outcomes and ongoing analysis of AEs.

So, overall when I consider risk/benefit in this, first of all, I think that efficacy-wise in my mind--I know that this drug works and it clearly reduces serum uric acid. I am impressed with its safety, recognizing the gravity of allopurinol hypersensitivity states. These are rare cases that were referred to but you don't have to see more than one case of true hypersensitivity syndrome to be humbled by this.

One of the points I would like to make is that in patients who have been enrolled in this, mild to moderate, which means patients with true hypersensitivity syndrome, Stevens-Johnson and TEM, are not candidates for this. There has been no upgrading of toxicity in the entire oxy experience. In other words, if you have a mild to moderate rash with allopurinol you get a mild to moderate rash and there has never been single case of hypersensitivity syndrome, Steven-Johnson or TEM,

reported. So, I think this favorably influences my willingness to subject patients to the prodrug of the drug that they have been hypersensitive to. Furthermore, I think this risk management program makes sense.

So, to conclude, for the patients that I have described to you, who are allopurinol intolerant, I have no other therapeutic alternatives for them and I think that this is a valuable drug. I think that the data that have been presented thus far, at least in what I consider to be my experience with this drug, has a positive ratio of benefits to risk. I do believe, having been through this compassionate use program for so many years, that the proposed risk management program will be a better program. It will make this more widely available to patients because many patients have dropped out of the oxy program when they have moved and they couldn't find a physician to do this, and it certainly will allow better monitoring of this overall issue. Thank you.

DR. GIBOFSKY: Thank you, Dr. Calabrese. We are a few minutes behind, however, in the interest of open discussion I would like to afford the panel the opportunity to ask questions of any of the previous speakers. If there are questions from the panel, we will entertain them at this time before we take our break. We will make up the time later in the session. Dr. Felson?

DR. FELSON: A quick question for anyone, I think Len Calabrese has laid out the design of the Phase 4, which sounds like a randomized trial with a placebo control, with a primary endpoint of number of clinical attacks, it sounds like. Why was that chosen as the primary endpoint, especially given the discussion we have heard so far about potential surrogates, as opposed to using uric acid?

DR. MOORE: Let me start with that. Basically, that was an extensive discussion we have had with the FDA on acceptable parameters. Clearly, we would have benefitted from discussion with this panel, but a part of the requirement for

approval of this drug is that we had to get a Phase 4 study under way. So, that is how we designed it. It seems a perfectly beneficial clinical outcome that one would reduce tophi and so that is the basis for the study design.

DR. GIBOFSKY: Dr. Hochberg?

DR. HOCHBERG: When we go through our training, those of us who train medical students, residents and fellows, we recommend that the serum uric acid be normalized often to below 5 mg/dl or 6 mg/dl. So, maybe somebody could comment on what is a clinically important reduction or a clinically meaningful reduction in serum uric acid for someone who starts at 10? You know, what does it mean to have a reduction of 2 mg/dl even if you are still having an elevated serum uric acid level?

DR. CALABRESE: Marc, I think that is a great question. First I would like to point out that in most patients treated with oxy we have been able to effect far more than 2. That trial is biased by the fact that drug escalation was stopped when they hit t 2 mg. In most patients that I have

treated we have got 3 or more.

Now, asking the question of what is clinically meaningful, I think that this is a subject of debate. You know, there are data from Ralph Shoemacher that suggest that even the mere fact of escalating frequency of gouty attacks may be seen before even normalization. I have been impressed by patients on oxy in whom we have maximized their dose, keeping them in the range of 6, 7 or close to 8, the frequency of attacks have been decreased. So, I think this is an issue that needs to be addressed in a clinical study that will correlate clinical outcomes with SUA. This hasn't been done in any rigorous manner.

DR. GIBOFSKY: Dr. Geis?

DR. GEIS: Do you have anything in the literature that says what if you gave placebo to a bunch of patients, what would their uric acid levels do? I mean, because this is open-label it is kind of hard to interpret it but do we know about historical data with placebo studies?

DR. MOORE: I think there is very little

literature data on that today. Clearly, we will be studying that in our Phase 4 study and have a much better handle on it then. But, as Dr. Snyderman pointed out earlier, gout is a progressive disease and so one would clearly expect it to get worse and not better. So.

DR. GIBOFSKY: Dr. Finley?

DR. FINLEY: Dr. Calabrese, when you are thinking about clinical endpoints, and you mentioned tophi reduction and you described your vignette, are we talking about size, the number, healing? How do we do that? How do we validate that between raters and those kinds of things?

DR. CALABRESE: I am just a clinical rheumatologist taking care of people with sore toes, and I will leave some of these discussions to the experts here. But my experience, even with allopurinol, is that, you know, you don't see these things disappear over time, but certainly there is an element of regression because I have seen these draining areas receding. You don't see that cheesy stuff through the skin. You see a decrease in

girth that could at least be palpated. What the best way to measure this is, I would leave that to others.

DR. GIBOFSKY: Dr. Moore or Dr. Calabrese, help me understand how a compassionate use program, where the drug is restricted, would be less effective or not as good as a Subpart H approval where the drug would be restricted under your risk management program.

DR. MOORE: Let me begin. Basically, our experience has been with the compassionate use program to date. It is a less than perfect collection of data. So, what we are looking at is a much more controlled situation, creating a patient registry, which we don't have with compassionate use. As you know, compassionate use is more at the prerequisite of the individual investigator and not the company. Whereas, with a company controlled environment, which would be the Subpart H, we get much better feedback on risk and side effects to the patients. We would also get less of this loss to follow-up issue. We would be

able to track the patients. So, I think I would feel that we would have much better control of what was going on.

DR. CALABRESE: I would just like to mention that in addition to a smoother bureaucratic process for the physician, it would be much easier to register into this than become an investigator and do this. The compassionate use program really did not include any type of formal physician or patient education and this actually has the requirement for a knowledge base that a third party would check off on, actually looking over these report forms. You know, over 20 years ago they are fairly embarrassing.

DR. MOORE: Thank you. One final point on that as well is accessibility for patients. For a compassionate use program people have to hear about a drug one way or another and it is very hard for them to get on this program. Whereas, if the drug is actually marketed, albeit on a very limited distribution program, they will know it is available, physicians will know it is available.

DR. GIBOFSKY: I take that point, but the concern in the back of my mind is if the drug is available, albeit in a limited distribution, is there not the concern that the drug will be used beyond its primary indication by physicians who may think, based on the data, that perhaps oxy is superior to allo and why not start with oxy?

DR. MOORE: That is an excellent question and that is one of our greatest concerns as we go into this. So, in fact, what we have is that as the physicians request the drug there will be a very formal form, and in the NDA we have all of this material described where there is not just education material but the physician will have to formally describe the patient, and there are criteria which qualify them for receiving the drug and part of this is double allo intolerance. So, I think it is a very restricted system and it is a very good way of controlling it.

DR. GIBOFSKY: Dr. Anderson?

DR. ANDERSON: I have a question going back to the design of the study that is currently

under way, and it has to do with the eligibility restriction that the patient has to have had at least 6 attacks in the previous year. I was wondering what is known about the distribution of number of attacks per year in gout patients and what drove that--you know, what made you decide that?

DR. MOORE: It is a matter of powering the study, frankly, and what we are looking at is that a lot of these people are sicker anyway because by the time you get to an allopurinol-intolerant patient population they have been trying other treatments for a long while. So, often many of them are very sick patients. It is not that difficult to find people who have 6-8 gout attacks a year. We have 6 patients right now who are ready to come onto this study. But really it is a matter of powering the study, showing the efficacy of the drug in terms of this clinical outcome and, at the same time, being able to compare this to lowering serum uric acid, how much it goes down and where it goes down to.

DR. ANDERSON: Can I just follow-up on that?

DR. GIBOFSKY: Sure.

DR. ANDERSON: This wasn't presented here but it was in the background material we have, it was indicated that you would need a hundred centers to find those patients, which seems to run a bit counter to what you just said.

DR. MOORE: No, no, if I gave the impression they are easy to find, I didn't mean that. What I should say is that we have access, of course, to all of the physicians who have been recruiting into a compassionate use program. We are the only people who distribute oxypurinol. So, it is easier for us to find these kinds of patients because we already have access to the physicians who have them.

No, my bet is that we will get about two or three patients per site. This isn't your average clinical study where you have one patient per month per site. This is going to be much more restrictive than that.

DR. GIBOFSKY: Dr. Geis?

DR. GEIS: You didn't present any demographic data about the patients that you did study. How do you know they are representative of the intended patient population?

DR. MOORE: I am not sure I understand the question.

DR. GEIS: I mean, in most clinical trials I have been involved in, you usually want to give the demographics and show this really does represent what the literature says the patients will look like.

DR. MOORE: Oh, I see.

DR. GEIS: I think in one of the documents that we were given in advance the ratio of males to females was really not different from what I heard historically is the ratio by gender in the gout patients. So, it made me think who are you really studying.

DR. MOORE: No, as Dr. Dickinson said earlier, first of all, this is a rather small patient population that we are looking at, the

allopurinol-intolerant gout patient population. Secondly, we have the largest database of anyone on these patients. So, we believe that our database on 612 patients truly represents the demographics of the broader patient population. We have anywhere from 5-10 percent of them right now.

DR. GIBOFSKY: Dr. Mandell?

DR. MANDELL: In 213 the numbers that you have, 9 of 77 by ITT had less or equal to 6. I understand it wasn't pushed to do that. Since most of us would be pushing, if we are going to be treating, the uric acid down probably lower than just the targeted 2 drop, what information do you have on the safety or efficacy of the drug used in that manner, pushed to really try to drop the uric acid level?

DR. MOORE: Let me start and then turn to Dr. Dickinson. The most information we have is from our compassionate use program where, as Dr. Dickinson described, we have gone up to 1800 mg. So, I think for safety we have good safety data for prolonged periods of time at very high doses.

For efficacy, clearly the Phase 4 program will fill in more of that, although we do have good data from the compassionate use program, as Dr. Calabrese described. We get lowering of 3-4 mg/dl with these higher doses. Remember that the 213 study was designed to reach the endpoint of 2 only. So, that was really limited titration.

DR. MANDELL: How many patients does that include actually at those high levels?

DR. DICKINSON: The average serum uric acid at start was 10.1. So, about half the patients had higher than 10 and half had lower than 10 as a starting SUA. The oxypurinol maximum dose in the 213 study was 800 mg. I believe there were 9 patients that went up to 800 mg. That was the limit on that study. Again, once a patient had dropped their serum uric acid, if they dropped it from 11 to 9 they were not eligible for any further dose escalation because they had achieved the endpoint in that study, which was a 2 mg/dl decline in serum uric acid.

DR. MANDELL: So, we don't have a lot of

patients actually treated with the higher doses here.

DR. DICKINSON: We do in the compassionate use program, which is a real-world program where there are patients with renal insufficiency, renal transplantations. We have a number of patients who have been treated with 1200 mg, 1400 mg, 1600 mg a day.

DR. MANDELL: Do you know how many those are?

DR. MOORE: The mean dose that was used in the compassionate use program was 372 mg and we are asking for approval up to 800 mg for this indication. The vast majority of patients were in the middle, between 300-400 mg so there was really a distribution curve down on the other side. But in that program were 533 patients. So, you have a large distribution with the majority being in the middle with 300-400 mg coming out on the slope. So, we do have data on high doses.

DR. GIBOFSKY: Dr. Bathon, do I see your hand up for the last question?

DR. BATHON: Yes, along that same line just as a follow-up to that, how then are you guiding physicians in the Phase 4 trial to dose the drug since you are using a clinical endpoint as your primary?

DR. MOORE: It is a titration study and that is the same way that allopurinol is dosed. So, they would go up in 100 mg doses over a 16-week period. There is a 2-week run-in placebo period and then an 18-week titration study. Of course, being that this is a double-blind study the serum uric acid will be read by an unblinded outside physician so that will be guided by that. The goal is to lower the serum uric acid to 6 mg/dl. That is the goal.

DR. GIBOFSKY: I would like to thank the presenters for giving us some additional food for thought this afternoon. At this point we will take our break for exactly 15 minutes and resume at 11:08 by that clock.

[Brief recess]

DR. GIBOFSKY: We are ready to begin.

Will all the panel members please take their seats and the audience find theirs? At this point we have a presentation by Dr. Lourdes Villalba, who is the medical officer for DAAODP of the Food and Drug Administration, and she will speak on oxypurinol for symptomatic gout in allopurinol-intolerant patients. Dr. Villalba?

Oxypurinol for Symptomatic Gout
in Allopurinol-Intolerant Patients

DR. VILLALBA: Good morning. The goal of my presentation is to show you data from a specific new drug application, an example as a starting point for discussion of clinical trial design issues in chronic gout. The proposed indication for this drug, oxypurinol, is a very specific one in a very specific population. But when you go through the data I would like you to think about how these data may apply to other drugs and trial design issues in general.

Allopurinol, as mentioned earlier, is the first-line treatment of hyperuricemia in gout. The active metabolite of allopurinol is oxypurinol and,

because of the short half-life of allopurinol and long-life of oxypurinol, it is believed that the pharmacodynamic effects of allopurinol reside in the oxypurinol moiety.

There is limited data on comparison of allopurinol and oxypurinol. There are some studies in the literature that have compared them. For example, there is a crossover study of allopurinol and oxypurinol in close to 100 patients but those studies were not adequate for comparison of the efficacy or the safety. In any case, the literature suggests that allopurinol is more efficacious in reducing uric acid levels as compared to oxypurinol. The limited data available in the literature really has not shown a difference in safety between the two.

We do have one pharmacokinetic study looking at the conversion of allopurinol into oxypurinol. This study was conducted by the sponsor as part of the NDA and is an open-label bioequivalence study of 42 patients that showed that the relative bioavailability of single dose

oxypurinol is about 30 percent that of allopurinol for the 100 mg dose. That means that a single dose of oxypurinol levels is equivalent to 58 mg of allopurinol. The pharmacokinetic characteristics of oxypurinol non-linear. Therefore, the data in this particular study shows that 800 mg of oxypurinol produced oxypurinol serum levels equivalent to 112 mg of allopurinol. This, again, is single dose. We do not have data on multiple dose conversion.

Allopurinol is generally well tolerated, however, up to 10 percent of patients present intolerance. Despite the fact that the drug has been used for decades, the mechanism of toxicity is not well understood. There is some toxicity that is immunologically mediated and 204 percent of patients present with hypersensitivity reactions, and that is the main limitation to the use of allopurinol. As already explained earlier, most of the events are skin reactions, mile to moderate, occasionally severe including Steven-Johnson and toxic epidermic necrolysis. Other hypersensitivity

reactions include fever, hepatitis, nephritis, hematologic such as aplastic anemia and thrombocytopenia, and a very rare form of the hypersensitivity syndrome, and 20 percent of the cases may be fatal, the allopurinol hypersensitivity syndrome which involves all of the above--skin, fever, hepatitis, nephritis. It is usually associated with eosinophilia. The mechanism is unclear. It seems to be type IV hypersensitivity mediated, T-lymphocyte mediated with production of cytokines, including IL-5.

However, there is also non-immunologic toxicity that involves mainly renal and liver toxicity. In animal studies, for example, the toxicity is mainly liver, renal and cardiac and the hypersensitivity syndrome is not reproduced in animals.

I distinguish between these two forms of toxicity, however, in the clinical setting sometimes it is very difficult to distinguish one from the other. For example, if we see a patient with transaminase elevations, unless there is also

a rash or fever or eosinophilia it is going to be very difficult to say that that was related to hypersensitivity or not. It is unclear whether the hypersensitivity reactions to allopurinol are directed to allopurinol, oxypurinol or other metabolite.

The literature suggests that allopurinol desensitization may be of use or may have a role for some patients with mild to moderate cutaneous intolerance. There are some case reports in case report series and the most persuasive one is one by in arthritis and rheumatism that reports a retrospective evaluation of 32 patients who received allopurinol desensitization for over a month period and then continued on allopurinol for a mean follow-up of 32 months. Of those 32 patients, 28 tolerated doses up to 50-100 mg daily and 21 of those patients did so without any adverse reaction and 7 of those patients actually presented with some form of cutaneous reaction that was managed with symptomatic treatment and by modifying the schedule of the desensitization program. Four

patients required discontinuation.

It is important to note that the serum uric acid levels went from 10.4 mg/dl at entry to 5.3 mg/dl at the end for those patients who tolerated allopurinol. Also, I would like to point out that there were patients with renal insufficiency included in this retrospective study, with a mean creatinine level of 2.8 mg/dl. It is also important to point out that there were no patients with severe intolerance included in this retrospective review.

Regarding oxypurinol, the sponsor has already talked about the compassionate use program. Oxypurinol has been available for patients since 1966 as part of the compassionate use program. The sponsor has collected a large amount of data from approximately 500 patients in an open-label manner. I would like to point out that it was not a study that was prospectively designed to evaluate the efficacy or the safety of oxypurinol.

This was actually a retrospective evaluation of patients who were seen over a period

of 40 years. That is why there is less than optimal documentation of, for example, allopurinol intolerance prior to entry, also the efficacy and safety during the study. Clinical laboratories were not systematically collected, were collected at the discretion of the investigator. There are missing data. For example, serum uric acid baseline levels were missing in 32 percent of patients and post-baseline levels were missing in 24 percent of patients.

Regarding the demographics, up to 30 percent of patients were missing the age or the ethnicity data. Also, 25 percent of patients were missing baseline creatinine data. Regarding the patient disposition, 28 patients were lost to follow-up. Therefore, data from this program, although encouraging, is not adequate to assess in a robust way the efficacy or the safety of oxypurinol.

Let me say that the day suggest that the drug is effective in reducing serum uric acid levels, and also that some patients develop who

develop allopurinol intolerance tolerate oxypurinol. However, that was not enough for marketing of the drug and the sponsor entered discussions regarding additional data needed for marketing. Protocol OXPL213 was started at the end of 1999, beginning of 2000. It is important to remember that this is an unmet medical need in a population who is at high risk of developing allopurinol intolerance and severe reactions; that this drug was already available in compassionate use. So, at that time and in that setting it was thought that a 2 mg/dl change in serum uric acid, used as a surrogate endpoint, would be something reasonable. In addition to the uric acid levels, the study needed to assess efficacy and, if successful, a post-marketing study would be conducted for evaluation of meaningful clinical endpoints.

This is the study design, and you may have an idea already because of the prior presentation. This was a prospective, open-label, uncontrolled dose-escalation study of 14 weeks. That was the

base study and it included 79 patients. Those patients who completed the study were offered to continue into the extension and 48 patients continued into the extension. The extension is still ongoing.

Entry criteria included patients with symptomatic hyperuricemia with documented allopurinol intolerance. Documentation could be a single episode of intolerance as documented by the primary physician or rheumatologist or, in addition to that, the patient could actually have a history of rechallenge or desensitization. One-third of those 79 patients approximately--there were 26 patients who had undergone rechallenge or desensitization.

The exclusion criteria, as mentioned earlier--those patients with severe prior reaction to allopurinol did not enter the study. The use of diuretics and uricosuric agents were also exclusion criteria. Regarding renal function status, patients with creatinines of 2 mg/dl or above and liver function tests of 3 times the upper limit of

normal or higher were excluded from the study. Again, I want you to think about all these entry criteria.

The treatment scheme, you already saw that this is a fixed dose escalation study, starting with 100 mg and going up to 800 mg daily according to the fact if the patient achieved or not the desired endpoint. Most of the patients, 60 percent of the patients were on the 300 mg dose and I believe 8 or 9 patients were on the 800 mg dose. The others were on doses in between. Of course, some patients received the 100 mg dose and presented with reactions and were discontinued but most of the patients were on 300 mg.

Regarding the endpoints, the primary outcome was the serum uric acid level. However, I would like to point out that there was not a central laboratory. That means that each site worked with different labs and those labs had a different normal range.

The primary analysis was a landmark analysis of comparison of the mean baseline and

mean final value of week 2, 13 and 14, and there were also measurements of serum uric acids at week 6 and week 9 for those who had not achieved a 2 mg/dl drop by week 6. The primary analysis was to be in the ITT population and it was to show a decrease of at least 2 mg/dl.

These are the baseline characteristics of the study. The mean age was 61 years. Fifty percent of patients were male. The mean serum uric acid was 10.1 mg/dl, with a range from 7.7-13.7 mg/dl. The mean creatinine at entry was 1.3 mg/dl, with a range from 0.8 to 2.2. There were 26 patients who had failed prior rechallenge or desensitization.

Regarding concomitant medication, 43 percent of patients were on colchicine, prophylactic colchicine; 6 percent of the patients were on low dose aspirin; 53 percent were taking diuretics, although this was one of the exclusion criteria for this study; and 49 percent of the patients were taking NSAIDs or COX-2 inhibitors.

Regarding prior history of allopurinol

intolerance, most of the patients had skin intolerance, 8 percent of the patients had skin intolerance, and 20 percent had other manifestations such as hepatic, renal, malaise, all 3 or fever. Again, these patients had mild to moderate allopurinol intolerance, and there were no patients with prior history of hematologic intolerance or severe skin or liver intolerance. The definition of intolerance for liver intolerance was ALT elevation of 2.5 to 5 times the upper limit of normal, and for renal it was BUN or creatinine 1.5 to 3 times the upper limit of normal. There was no requirement for these to show eosinophilia. I mean, the word of the investigator was taken who thought these were allopurinol intolerance reactions.

The results of the FDA analysis are a little different from the sponsor analysis. In the ITT population at 14 weeks--and we looked at the 79 patients, all patients who were included in the study and received at least 1 dose of medication--the mean change from baseline was 1.78 mg/dl. In

the sponsor's analysis, in 77 patients it was 1.9 but in 79 patients when they looked at the whole thing it was 1.85. But, actually, that doesn't matter too much. I think that the important thing here is that the study did not achieve the primary efficacy endpoint. But even if it, let's say it achieved 2 mg/dl, the issue is if 2 mg/dl is something that one would like to see as the goal for treatment for gout.

In the completer analysis the change in 54 patients was 2.32 mg/dl. This change was highly statistically significant, with a p value of 0.001. That means that the study rejects the null hypothesis that the change of serum uric acid level associated with oxypurinol is equal to zero.

Another way of looking at the data is by looking at final mean serum uric acid. In the ITT population it was 8 mg/dl. In the completer population it was 7.5 mg/dl. By our analysis of the data set, 10 patients achieved a serum uric acid level of 6 mg/dl or below and 2 patients achieved 5 mg/dl or below. This is the most

important difference, I would say, that I found with the sponsor presentation. We have not clarified yet why there is this difference. We have to go through the data set again with the sponsor probably.

There was no evidence of dose response and that may have something to do with the study design, the fixed dose escalation. Another factor that may have something do with it is the pharmacokinetic characteristics of oxypurinol. As we saw, that is non-linear in a single dose and we don't know the data for multiple dose.

There were 12 flares and 8 of them were during the base study; 5 only during the base study and 3 of them in the base and extension, and 4 were only during the open extension. Four patients had tophi complications, such as infection, drainage or pain, 2 in the base study and 2 in the extension. In the absence of a placebo-control arm this is very difficult to interpret. Is this oxypurinol effect on serum uric acid or is this spontaneous flare that occurs despite the drop in uric acid?

We looked at the characteristics of the patients in the base study. All patients with gout flares dropped their uric acid levels, and the range was from 1.5-3.9 in some patients. So, there was a drop of uric acid level. Half of the patients were on colchicine. None of the patients were discontinued from the study. They were treated with steroids or NSAIDs and continued and completed the study. I don't have the data from the extension. The extension is still ongoing so data is incomplete.

I am going to show you a few slides about the safety. There were 5 deaths. One during the base study. That was a pancreatic carcinoma. There were 4 during the extension. One patient died of end-stage liver disease; one was found dead. One patient had GI bleeding and worsening COPD, and one patient died of sepsis after a surgical procedure. All these events, in the opinion of the investigators, were unrelated to study drug.

Regarding serious adverse events, non-fatal

serious adverse events, there were 7 in the base study and 15 in the extension. Again, all of them seemed to be unrelated to study drug. I would like to point out 2 definitive myocardial infarctions and 1 questionable myocardial infarction in the base study. So, we see 3 patients with cardiac events in a 14-week study of 79 patients. Maybe this finding may be related to the cardiovascular high risk population that is under study with the co-morbidities and associated factors like hypertension, obesity and diabetes seen in patients with hyperuricemia, and also hyperuricemia itself may be an independent risk factor.

Regarding discontinuations, 54 patients completed so 25 patients discontinued. Of those discontinuations, most of them were due to skin intolerance. Sixteen patients discontinued because of skin intolerance. One patient was reported to have discontinued because of liver intolerance. One patient had thrombocytopenia. We had the pancreatic carcinoma and one patient was a protocol

violator, and there were 5 cases that I classified as miscellaneous and I would like to expand a little bit more on these.

One of the patients was discontinued because of monitor decision. After one dose of oxypurinol, this patient developed a fever, followed by chills, skin sensitivity, polyarthalgias and viral syndrome. This patient was excluded from the sponsor's analysis because it was considered unrelated to study drug. However, I think that it may have been related but, in any case, in an efficacy ITT analysis I think it should be included in the analysis.

One patient had a hypersensitivity syndrome. It was described as hypersensitivity NOS. That means no other symptoms and there is nothing more in the case report form. So, it isn't clear exactly what the reaction was of this patient.

One patient had fever, chills, headache and allergic rhinitis, probably unrelated. One patient discontinued because of nausea and vomiting

after one dose and this patient had a prior history of liver intolerance.

One patient developed elevation of ALT and BUN and it was considered by the investigator to be a protocol violation because the patient was not complying with the medication. So, this may be unrelated, this elevated ALT, but still should be included in the analysis of safety.

In addition to the patients who discontinued, there were 3 patients who completed the base study but had hypersensitivity reactions and did not enter the extension. Two of them had liver function test elevations and one had a rash.

Therefore, in summary, approximately 30 percent of patients developed intolerance; 70 percent of patients with intolerance showed skin intolerance--I am talking approximately, I am not giving an exact number--70 percent within the first week. Most of the patients showed the same kind of intolerance as before and none of them was considered serious. There were 2 cases that were different from baseline, 1 with thrombocytopenia

and the other with LFT elevation.

This slide focuses on the patients who had actually undergone and failed rechallenge or desensitization. There were 26 patients. Of these patients, 10 discontinued because of hypersensitivity reactions again. The hypersensitivity reactions were the same as they had in the prior allopurinol experience. That is 40 percent of the patients. There were 3 deaths, 1 in the base study and 2 in the extension, and in the extension that included the patient with end-stage liver disease and 1 patient with sepsis.

Therefore, in summary, 79 patients were enrolled; 54 completed the 14-week study; 48 entered the extension. At the time of the analysis there were 37 patients available in the safety population. Ten patients achieved serum uric acid levels of 6 mg/dl or below and 5 mg/dl or below at 14 weeks. Eight patients had flares during the base study.

Regarding adverse events, there were no serious hypersensitivity reactions. Most of them

occurred within the first week. Most of them were cutaneous and similar to what the patient had presented before. Others, beside the skin, included a few liver intolerance events; 1 thrombocytopenia; 1 viral syndrome. This was in a population of patients with mild to moderate intolerance to start with and with normal renal function or mild renal insufficiency.

Therefore, our challenge is to define a population for a favorable risk/benefit in which a modest decrease in serum uric acid would outweigh the risk of 30-40 percent intolerance in a population which is at increased risk of intolerance and in the setting of a not well-defined clinical benefit.

So, all these data are for you to take and help us in the discussion of the discussion points. That is the end of my talk.

DR. GIBOFSKY: Thank you, Dr. Villalba. Are there questions for Dr. Villalba? Dr. Hoffman?

DR. HOFFMAN: That was very helpful. I was going back to the data that you showed us that

concluded that there was no evidence of dose response.

DR. VILLALBA: Yes?

DR. HOFFMAN: I was curious about the rigor with which we come to conclusions about that data because there were only 54 completers in that trial, and it wasn't clear--well, we didn't see the data on how many patients were at each dose level and followed for what period of time, perhaps up to 14 weeks, perhaps longer, for us to know whether or not there was adequate sample size at each dose level to really address dose response. If it not adequately addressed in this study, do we have from the applicant additional data about dose response? Do we also have the necessary data about dose response in allopurinol to come to conclusions about linearity of dose response?

DR. VILLALBA: Well, regarding the data from the sponsor for oxypurinol, yes, we did the analysis and we looked at the sponsor's analysis with the data that we had. I can say that it cannot be said that there is a dose response. I am

not saying that there is no dose response. That is the database that we have.

DR. GIBOFSKY: Dr. Villalba, please use the microphone. It is a bit difficult to hear you.

DR. VILLALBA: I am sorry. So, that is the database we have and I think it is inadequate to address that.

DR. HOFFMAN: I think it is a terribly important issue if we are talking about a new protocol in which our goal is to achieve a uric acid of 6 or less by dose escalating. If there is really no dose response, I think we need to clarify that before we feel comfortable about a protocol that uses a dose escalation strategy.

DR. VILLALBA: Yes, I agree.

DR. GIBOFSKY: Dr. Geis?

DR. GEIS: In your analyses did you look at changes in other risk factors which could affect uric acid levels, like blood pressure, weight, alcohol use, thiazide changes?

DR. VILLALBA: We looked at concomitant medications. We didn't look at other factors but

regarding concomitant medications--let me think--there were 8 patients who were started on NSAIDs or COX-2 inhibitors but I don't think that would affect the serum level but it may affect the symptoms. There were 2 patients, I believe, that started new diuretics but there was not much change other than that. And, 4 patients started colchicine in the study.

DR. GIBOFSKY: Dr. Mandell?

DR. MANDELL: Following further really on the question of the pharmacokinetics and pharmacodynamics of the drug, in looking at trying to get a dose response in the multi-dosing setting, was creatinine clearance taken into consideration in that analysis or are the numbers too small, number one, really relating to the pharmacokinetics of why there might or might not be a dose response? Two, do we know anything about the pharmacodynamics in patients who are allopurinol sensitive as opposed to non-allopurinol sensitive patients on the sensitivity to oxypurinol?

DR. VILLALBA: I don't think we have any

data on that. Regarding the first question, the data we have on pharmacokinetics is only single dose. There is no data on multiple dose.

DR. MANDELL: So, what you said about the non-dose response was the single dose analysis?

DR. VILLALBA: No, no, that was in the study, the result of the study.

DR. MANDELL: So, some of those patients had various levels of creatinine clearance in there?

DR. VILLALBA: Yes, but as per the entry criteria, only patients with creatinine up to 2 mg/dl could enter and the mean creatinine at entry was 1.3.

DR. MANDELL: There is a wide spread of clearance.

DR. VILLALBA: Yes, but we don't have data on clearance.

DR. GIBOFSKY: Dr. Anderson?

DR. ANDERSON: My concerns are only partly to do with safety. I found it very disturbing that the study was not placebo controlled because, as

you commented earlier, in the absence of a placebo control or any kind of control you really cannot interpret the safety results and even the efficacy results. It is not clear from other discussions that have been held here whether a drop of 2 mg is clinically important and, given the lack of knowledge about the reliability of this measure, is it even a minimally important difference? It could be that you need at least 3 mg or, if you are starting high, 10; you need to have an even greater milligram drop for it to be clinically important.

I guess those are just concerns that I have about the study, and also about the revised analysis, the revised analysis that was presented by the sponsor. You know, this was an analysis that was devised after the initial analysis didn't quite work. So, those are all concerns I have.

DR. VILLALBA: Yes, regarding the first concern, we agree completely. That was our concern all along and the sponsor's concern too. That is why it was agreed that a Phase 4 study would be conducted. Regarding that change, it is precisely

what we wanted to decide because that is our issue too. We are not sure that 2 mg/dl should be considered acceptable as adequate evidence of efficacy.

DR. GIBOFSKY: Dr. Boulware?

DR. BOULWARE: Regarding study 213, I am sort of bothered by drawing conclusions about dose responsiveness and the ability to hit the endpoint of 5 mg/dl or 6 mg/dl which we considered desirable when the study was designed, that you stop the dose escalation once you dropped by 2. When I think about that and I looked at the earlier spaghetti gram provided to us by the sponsor, the number of patients entered who had a baseline SUA within 2 points of the desired endpoint are very limited. There are only about 2 or 3 patients. Anyone who had a drop of 2 from their baseline had their dose stopped. So, it is very difficult, in my mind, to draw any conclusions about its inability to be dose responsive and also its inability to achieve a target of 5 mg and 6 mg. Is that appropriate?

DR. VILLALBA: I completely agree with

you.

DR. GIBOFSKY: Dr. Hochberg?

DR. HOCHBERG: I would like to get your comments about safety. I am a bit concerned, and let me refer to a couple of your slides. First, the proposed indication, which is your slide number 3, is for treatment of hyperuricemia in patients who are intolerant and have failed either rechallenge or desensitization with allopurinol. In the 213 study, in your presentation only 26 of the subjects had actually had a prior rechallenge or desensitization so the majority had not.

It appears to me that there is an imbalance in the incidence of adverse experiences during 213, with a higher rate of adverse experiences in those who had failed the prior rechallenge or desensitization than in those who had not had the desensitization or rechallenge. The one death that occurred during the study occurred in someone who had failed the rechallenge or desensitization. Half of the deaths during the follow-up extension occurred in that population.

So, does the lack of data, relative absence of data in the people who actually would fulfill the criteria for this indication concern you?

DR. VILLALBA: Yes, and I agree with you.

DR. GIBOFSKY: Dr. Felson?

DR. FELSON: I guess I am going to pose this to you but I would also be happy to pose it to the sponsor, the idea that you get exactly the same side effects if you get oxypurinol reaction and that the bioavailability of oxypurinol is substantially lower than allopurinol might suggest--and also that there is a good deal of literature suggesting that the side effects of allopurinol are often oxypurinol-mediated--that might suggest an explanation of oxypurinol efficacy, that it is simply administering lower dose allopurinol. Why not just give lower dose allopurinol? Is that an explanation that is consistent with the data presented?

DR. VILLALBA: I agree with your concern. That is all that I can say.

DR. GIBOFSKY: Are there further questions

from the committee? If not, at this point let me make one brief announcement. Several members of the committee have asked for additional information to educate themselves, so we can do our job, about Subpart H. As alluded to by Dr. Witter, 21 CFR 314.510 etc. I suspect many of my colleagues are not adapt at reading the Code of Federal Regulations so I have asked Dr. Harvey to please provide us, sometime over the next 24 hours, with either the website where that can be perused at leisure--if anyone peruses the CFR at leisure--as well as perhaps an executive summary and some examples of where Subpart H has been invoked. With that, we are at lunch. We will resume at exactly one o'clock.

[Whereupon, at 11:49 a.m., the proceedings were recessed for lunch, to resume at 1:00 p.m.]

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

DR. GIBOFSKY: Thank you, we will now begin the afternoon session. Before we begin the public hearing we have a couple of administrative matters. Dr. Harvey has completed his homework assignment that I gave him before the break and he would like to present some comments to the committee. Dr. Harvey?

DR. HARVEY: Thanks very much. I just wanted to give you a quick blurb on Subpart H. Actually, I really don't want to go into too much detail but I want to be able to give you the information you need to go and read all about it. My memory did serve me correctly, there was a panel meeting, an Oncological Drug Advisory Committee meeting on March 12 and 13 of 2003 where they actually spent a whole day on Subpart H. So, you can see that this is an area where, if you wanted to go into some depth, you could really spend literally a whole meeting just on Subpart H.

The transcript of that, the summary, all the related material is on the website. So, for

those of you who are not initiated to the web, you just go to the FDA web page, so www.fda.gov and you get the main page. There is a little box up on the upper left-hand corner where you can actually do a search. In this case you just put in Subpart H. If you just put in that simple term, Subpart H, you will get everything in the world you want to know and, luckily, the first hit on that search is actually a printout of all of the NDAs that have ever been approved by FDA under Subpart H. As I said this morning, the vast majority of those are in the areas of HIV treatment where viral load was the surrogate endpoint, and the other area was oncology, as I said this morning, where tumor response and variations in tumor response themes were used as a surrogate endpoint.

So, really that resource, which is publicly available, is really the best way to go ahead and get your hands around the whole issue of Subpart H. Really, in light of today's discussion, it really is just sort of a peripheral part of what we are discussing, which is really the clinical

aspects of clinical trial design and your expertise in the area clinically as well as scientifically. But I wanted to get you that information and that is really the best resource to answer that question.

DR. GIBOFSKY: Thank you, Dr. Harvey. Before the break there were some questions addressed to the sponsor, Cardiome, and, unfortunately, my back was turned and I did not see them raise their hand. There was a specific question I believe from Dr. Felson to them. So, in the interest of collegial discourse I extend my apologies for not recognizing that they had a comment to make and would ask them to respond to some of the discussion this morning. Dr. Moore?

DR. MOORE: No apology is necessary but thank you very much for giving us the opportunity. We are going to show you very quickly some data that addresses the issue on rechallenge versus non-rechallenge patients, and I will make a comment on PK values as well. Dr. Dickinson?

DR. DICKINSON: Can I have the slide? One

of the questions that arose is the dosing in patients in the CUP program. This just gives you the range of doses. As you can see, the range is from less than 100 and, in fact, goes up to 1800 and this is the range of dosing. So, is pretty broad. Not everybody is at 300 mg, and it tends to be higher than 300 mg, as you see, with allopurinol.

The next slide. The other question that came up was about allopurinol rechallenge. In fact, we did have information on 97 percent of all our patients, whether they had been rechallenged or not. Approximately 38 percent had been rechallenged and the remainder, 62 percent, had not. When we looked at safety data here we could find no difference between these groups. When we looked at the data in 213 as to whether or not these patients could tolerate oxypurinol, it was exactly the same, 28 percent could tolerate oxypurinol whether they had been rechallenged or whether they were just considered to be intolerant on the basis of the usual one clinical reaction to

allopurinol. So, we didn't find that the information about rechallenge was particularly helpful. Thank you.

DR. MOORE: Finally, a comment on the PK, is oxy low dose allo? In fact, the usual literature statement is that oxy is half as bioavailable as allopurinol. We have a chronic dosing study in congestive heart failure where in 31 patients we have measured the blood levels to 600 mg to oxypurinol and that is 11.3 mcg/ml. What you would expect from 300 mg of allopurinol is between 6-10 mcg/ml. So, again, 600 oxy equals 300 allo seems to hold and we agree with Dr. Villalba that we think those results were an artifact of the single dose that was given on the PK. I mean, we did it and those were the results but chronically it looks quite different. So. Thank you very much.

DR. GIBOFSKY: Thank you. One small administrative item, more for the guests in attendance than the members of the committee, outside there was a sheet showing the list of

tentative meeting dates for the Arthritis Advisory Committee being 10/21 and 10/22/04. Staff was made to realize several weeks ago that that is in conflict with the American College of Rheumatology meeting and so we are currently canvassing the committee to determine when an appropriate next date will be. As soon as that determination is made it will be posted on the website for those of you who are interested in attending that meeting, but it will not be October 21 and 22 as posted on the sheet outside.

We are going to move into the open public hearing section at this time. Before we begin I would just like to read a statement into the record. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you,

the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Our first speaker in the open public hearing session is Mr. Edward G. Mihalo. Mr. Mihalo?

Open Public Hearing

MR. MIHALO: Good afternoon. My name is Ed Mihalo and I am a pharmacist in the Pittsburgh, Pennsylvania area. Cardiome has said that they would pay me for travel and some lodging.

Besides being a pharmacist, I am a gout patient and I currently use oxypurinol since I had an allergic reaction to allopurinol. To fully understand how my quality of life has improved, you need to know a little about my history. I had my first kidney stone at age 20. I continued having stones periodically until urologist prescribed allopurinol. My serum uric acid was already well over 10 mg/dl but I had not yet experienced gout.

Three to four weeks into the treatment with allopurinol I developed a rash from head to toe. The allopurinol was discontinued and I was treated with diet and increased fluid intake alone. By age 35 both gout and kidney stones were causing me a great deal of pain and suffering on a regular basis. My wife and kids also had to endure my pain and depressed moods. They watched me crawl into the house because I was in such pain. I had to go to work on crutches, which didn't help because one gouty foot touched the ground and it does hurt. My co-workers tried to help by moving me around the pharmacy on a chair so I could get from station to

station.

Finally, I was led to a rheumatologist who had heard of oxypurinol. My treatments up to this point included steroids, NSAIDs, mild narcotics and colchicine which caused me great gastrointestinal distress. For about eight years I was on oxypurinol and I was well controlled both for gout and kidney stones.

Unfortunately, when I was 43 my physician moved out of the country and I could not find anyone to replace him and the oxypurinol. There was an immediate backslide into gout attacks, kidney stones and incapacitating pain. At times I would pass more than one kidney stone a week and have a gouty attack concurrently. The incidence of gout episodes was increasing as well as the duration of the attacks. The kidney stones went from the size of tiny grains of sand to something that resembled small sea shells. I began collecting the stones and in this small plastic bag which contains about 40 stones in that period just between the first treatment and the second--I

thought soon I would have enough for my own private beach--

[Laughter]

--but I wouldn't have been able to enjoy it anyway. Believe me, there was no joy in life during these attacks. It was during these years without oxypurinol that I seriously thought that amputation might be a better alternative to dealing with the excruciating pain. Then I had a severe episode in my knee so now I couldn't even crawl around the house. Also, two of my fingers began to develop tophi about the size of peas.

About three years ago my daughter located Cardiome Pharma through an Internet search. They helped me to locate a physician in the area who had experience in treating a patient with oxypurinol. He agreed to help me and now I can stand here to speak to you pain-free. My serum uric acid is normalizing so gout attacks have ceased. I haven't added a kidney stone to my collection, which has reduced my fear of impaired kidney function. The tophi on my fingers are disappearing.

Additionally, I have had no rash or unusual blood work.

Without oxypurinol I merely existed. I had no quality of life. I had reached the point of desperation of many times. Now oxypurinol has given me my life back. I am able to perform my job as any professional would. I can also enjoy all the social activities that I had in the past, and I am grateful for the supply of oxypurinol and I would like to thank all of you for being attentive to my story.

I have also been asked to read a letter from--You can come back for that.

MR. MIHALO: Come back for that? That is fine. Thanks very much.

DR. GIBOFSKY: Thank you, Mr. Mihalo. Our next presentations are going to be delivered jointly, sharing some time, by Dr. Nancy Joseph Ridge and Dr. Jane Osterhaus. They will be sharing 15 minutes.

DR. JOSEPH-RIDGE: Thank you and good afternoon. My name is Nancy Joseph-Ridge. I am a

rheumatologist and I work at TAP Pharmaceutical. We are currently designing a clinical program looking at a new xanthine oxidase inhibitor so we would like to share our view as a proposed clinical trial design for chronic gout.

As you heard this morning, the treatment of hyperuricemia is indicated for gout; tophaceous gout; and also renal calculi due not only to uric acid but also calcium oxalate. The goal, we believe, is to reduce and maintain serum urate to less than 6 mg/dl--fairly well published and documented.

I want to just go over a couple of literature reports on observational studies that have been done. The first one is by Lee Yu and Dr. Schumacher from Pennsylvania, in General Rheumatology in 2001, looking at the treatment of hyperuricemia in patients with gout treated with allopurinol. This was 57 subjects treated prospectively for 10 years.

There were 2 groups divided from serum urate of less than 6 mg/dl and those that were

greater than 6 mg/dl. Those with less than 6 were noted to have reduction in tophi and tophi were greater in those greater than 6, with 37 percent of the subjects versus 16 percent of the subjects when their serum urate was less than 6. Fewer crystals were noted in the joint fluid of the aspirates in 44 percent of subjects with less than 6 mg/dl versus 88 percent.

Then, something that we have been talking about today, fewer gout attacks over a period of 2 years, and that went from a mean gout attack of 1 attack per year versus 6 attacks per year when serum urate was greater than 6 mg/dl. So, we see these three outcomes looking at reduction of serum urate.

The next publication I would just like to highlight is one from Perez-Ruiz. This was in Arthritis Care Research, in 2002. He actually looked at 63 patients who were treated with allopurinol, benzbromarone or a combination of both. What he did was look at tophi and measured then using calipers to see how fast they reduce.

The mean duration of tophi resolution actually was 20 months and the time span was anywhere from 6 months to 64 months for the tophi to totally resolve.

What he noticed was that the resolution rates of those tophaceous deposits were directly related to how low your serum urate level was. With allopurinol there was a 0.57 mm/month resolution with a serum urate mean rate of 5.37. Benzbromarone decreased tophi by 1.21 mm/month when the serum urate was 4. With combined hyperuricemic activity of both agents in combination, 1.53 mm/month and the serum rate was 3.97 mg/dl. So, a direct correlation between decreasing serum urate with reduction of tophi.

What we have seen in our current clinical trials and what we are proposing as clinical trial design for chronic gout is for the primary endpoint to be the maintenance and reduction in serum rate to less than 6. This is key and may take a while before you can see clinical benefit up to one year or maybe longer because of total body urate load

having to be decreased over that period of time.

The second endpoints being those of clinical endpoints in tophi reduction. These measures via either imaging MRI, ultrasound or the way that Dr. Perez-Ruiz did using either calipers or physical measurement. Reduction in gout flares over a period of time, which would be a long-standing gout flare reduction over at least a year period. Inclusion of a comparator to look at safety and efficacy of allopurinol and/or placebo. Placebo is very important to look at adverse event background rates, with adverse events being noted with concomitant drugs that we give, such as colchicine, NSAIDs or the other concomitant drugs that our subjects have to be on. Minimally to demonstrate equivalence to comparator is also key. We also think that we should consider a safety dose which would be 2 times the maximum clinical dose to give you that idea as far as the adverse events.

Finally, long-term controlled studies, at least one study having a one-year duration. The older literature with carbon-14 radiolabeled uric

acid shows that it takes at least one year for total body urate loads to sometimes normalize and those subjects with tophaceous deposits may take longer.

The study population should resemble the gout population and include renal impairment and those with other co-morbidities, and finally, a proportion of subjects with higher baseline serum urate or seeing with epidemiology data that higher baseline serum urate is a factor and that efficacy and safety of the drug should be analyzed with that.

DR. OSTERHAUS: Good afternoon. Jane Osterhaus, I am a consultant to TAP in the area of health outcomes. It has clearly been touched on a lot already this morning, but I would like to encourage the committee to consider the necessary inclusion of humanistic information in gout clinical trials. With the renewed interest in gout treatments--we heard that there hasn't been a new treatment in about three to four decades almost, so I think we have this new increased interest in

gout. We also have heard this morning that the prevalence of gout in the U.S. is certainly expected to increase due to the aging population, obesity, increasing rates of type 2 diabetes.

Coupled with the new interest in gout, I think we have also learned a lot over the last decade or so about patient-reported outcomes and their importance in medical decision-making. When I think about patient-reported outcomes I am talking about health-related quality of life, work productivity, functional status--things that are quite important I think to the rheumatology community.

Currently there is no existing guidance on patient-reported outcomes for gout clinical trials, but if you think about gout and what we know about it, it certainly isn't a silent disease. We have pain. We have heard about swelling, tophi and some of the long-term potentially emotional consequences of gout as well. Given that, I think it is reasonable to consider measuring outcomes such as patient functioning, well-being, symptom relief and

satisfaction with treatment.

The types of measures that you can consider recommending or including in clinical trials range from general health status instruments such as the SF-36 to disease specific ones. The SF-36 I think would be a very reasonable choice for a general health status assessment. It is certainly well-known in the clinical trials community. It is probably the most commonly used health status measure that is a general measure. Its reliability and validity are certainly well established and, certainly, if you think about the rheumatology committee it has certainly been used in osteoarthritis and rheumatoid arthritis trials. We also can compare across conditions.

In terms of disease-specific measures, the HAQ is, again, a very frequently used and widely recognized instrument that is used in RA clinical trials. It has 8 domains and it may be useful in got, although its usefulness may be limited by the joints of the gout patients that are actually affected. So, HAQ may or may not have some

validity in a gout population.

We have identified no disease-specific gout measures in the literature and we thought that it did make sense to probably think about an instrument that actually focuses on specific aspects of gout that are not captured in general instruments like the SF-36. So, TAP has developed a gout assessment questionnaire that currently consists of 21 items and 7 domains. We just have some information based on 2 cross-sectional data sets. Within that cross-sectional setting we see good internal consistency, and we see adequate reliability for its initial use but there is clearly work that needs to be done on going. We need to confirm the hypothesized scales. We need to gain some experience in different gout populations and we really need to understand the relationship between the measures in the GAQ with clinical measures that people have talked about today. We also need to understand things like minimal clinical important difference and change over time.

If you are going to be including humanistic measures in clinical trials, it also makes sense to think about the timing of those measures. Given the comments that we have heard earlier that the initiation of gout therapy might result in more acute gout flares early on and that it could take up to a year for total body urate load to decrease to normal, we would recommend that for patient-reported outcomes you evaluate longer-term data with considering the impact of gout treatment from patients' perspective as opposed to very short-term data. Thank you.

DR. GIBOFSKY: Thank you, Dr. Osterhaus. We will next hear from Dr. Zeb Horowitz. Dr. Horowitz?

DR. HOROWITZ: Members of the advisory panel, members of the FDA, ladies and gentlemen, thank you for this opportunity to make a brief statement to the committee about issues we face in the design of clinical trials for pipeline product for refractory gout patients, puricase.

Puricase is a genetically engineered

recombinant porcine urate oxidase that we are developing to control hyperuricemia in patients with severe symptomatic gout in whom conventional therapy is contraindicated or has been ineffective. This recombinant uricase has been modified by covalent detachment of methoxypolyethylene glycol, which is expected to extend the duration in the circulation and to reduce the potential for immune response.

In a Phase 1 study conducted at Duke University, intravenous puricase appears to be effective in achieving a dramatic and a prolonged reduction in circulating uric acid to sell below the solubility limit. A Phase 2 trial is ongoing to confirm and extend these results.

We anticipate that rigorous and continuous control of hyperuricemia throughout the dosing interval is achievable in most patients with otherwise refractory gout. Currently approved agents for the treatment of chronic gout have demonstrated efficacy in lowering circulating uric acid but have no definitive evidence regarding

their effect on long-term clinical outcomes.

It is our hope that chronic administration of puricase may prevent or eliminate the accumulation of uric acid in joints and tissues that leads to acute gout attacks and other long-term consequences of chronic hyperuricemia, including destruction of joints, bones, cartilage and tissue. However, demonstration of these clinical benefits within the context of a registration program is impractical at this time. We believe that the continuous control of uric acid well below the solubility limit is the appropriate registration endpoint for this product.

Major hurdles must be overcome before a rigorous, well-controlled clinical endpoint trial can be implemented in patients with refractory gout. Some of these hurdles are heterogeneity of patient symptoms in relation to circulating concentration of uric acid; lack of reliable information relating rate of change of circulating uric acid to symptoms; unpredictability of gout flare frequency and severity; lack of a validated

disease-specific instrument to assess clinical severity and change; lack of a validated methodology to assess tissue stores of uric acid quantitatively; lack of a validated methodology to assess gout tophi quantitatively; and, finally, ethical concerns about placebo-controlled design in long-term clinical trials in refractory gout patients even though these patients are already inadequately treated with available therapies.

In view of these hurdles in trial design for the treatment of refractory gout, what is the most appropriate efficacy endpoint in pivotal trials today? The circulating concentration of uric acid is the most reliable measure of drug efficacy in hyperuricemic gout patients for whom conventional therapy has failed to control disease, or who are unable to use alternative therapies due to intolerance. These refractory gout patients have chronic hyperuricemia even while using allopurinol or uricosuric agents. Such patients suffer chronic, debilitating pain and deformity. No spontaneous remissions occur.

We know that chronic hyperuricemia leads to tissue accumulation of urate, but we cannot directly correlate the degree of urate accumulation with the effective drug treatment on urate accumulation with clinical outcomes.

Puricase offers the possibility of continuously and dramatically lowering circulating uric acid levels on a chronic basis. We have observed puricase to do this in the first day of administration of a single dose, and to maintain a very low level for up to one month. We anticipate that very low levels of uric acid can be maintained on a chronic basis in most patients upon multiple dose administrations at multi-week intervals.

The effect of puricase on tissue levels of uric acid is unknown. We hypothesize that over periods of time, perhaps long periods of time, tissue deposits of uric acid can become gradually mobilized into the circulation where puricase will safely destroy it. Over months or years a beneficial reduction in painful symptoms of gout may become observable in otherwise refractory gout

patients. The number, volume and symptoms of gout tophi may become reduced.

As long as the maximum concentration of circulating uric acid remains continuously below a very conservative threshold, perhaps less than 6 mg/dl, over a long period of time it is reasonable to expect a highly favorable clinical outcome. But we cannot predict when and in what specific way these benefits will accrue. In this context, we believe that the most appropriate efficacy endpoint for pivotal trials of a new agent, as effective as puricase is in lowering the circulating uric acid concentration, is the circulating acid concentration. Thank you.

DR. GIBOFSKY: Thank you, Dr. Horowitz. Dr. Horowitz is senior vice president and chief medical officer of Savient Pharmaceuticals, Inc. in East Brunswick, New Jersey. Our next presentation will come from Mr. Edward Mihalo, reading a statement from Mr. Walter J. Clifford who is unable to attend due to travel problems. Mr. Mihalo?

MR. MIHALO: I am Walter Clifford, a

resident of Colorado Springs, Colorado, where I reside with my wife of 37 years. We are the parents of 8 children. I will shortly be 60 years of age. My academic training and professional work are in the areas of immunology and microbiology. I own and operate a small specialty lab which provides immunologic clinical testing and research. Although I have been aware that gout has been a problem to members of my extended family for several generations, I did not personally recognize the problem in myself until approximately the age of 45 years.

Our family has an atypical manifestation of the condition which strikes in the ankles, knees, hips, shoulders, elbows, wrists and hands but very seldom in the great toe. Fluid aspirates from the wrist, elbow and knees have demonstrated the abundance or classical uric acid crystals. The outward manifestations of regional swelling, hot, red tissue and severe restricted mobility have all been present during flares.

Initial treatment with indomethacin and

colchicine were ineffective. For a period of about six months allopurinol seemed to help. However, I developed the classical allergic response to the allopurinol, including swelling, hives on the torso, back and face, elevated heart rate and difficulty in breathing. Intolerance of allopurinol required intermittent prescriptive doses of benadryl and other histamines under the direction of an allergist. Clinical effectiveness of the allopurinol diminished until it was finally discontinued altogether.

Gout flares became frequent and severe and could only be controlled with methyl prednisolone in Medrol tapered dose packs. The Medrol is usually restricted to three or at most four uses per year. However, my condition became severe enough that packs were used every four to six weeks and, on a few occasions, back to back. My rheumatologist worked with me to manage diet and other considerations, as well as to try various approaches to control the gout.

Nothing seemed to make much difference in

either frequency or severity of the flares. As I began to lose mobility of my hands and wrists, it became harder and harder to work at my profession and in the lab. The flares in my knees and ankles made it difficult to safely drive the car and I became dependent on my wife to drive me where I needed to go. I very seriously began to search for an alternative as the flares became more frequent and severe.

When my doctor approached me about taking part in a clinical trial study involving oxypurinol I eagerly agreed in the hope that something might be found to help me. I began the study in July, 2000. Within a few weeks I began to find substantial relief from the gout and immobility. Since time I have only had two flares, both of which were substantially shorter and more moderate than previously experienced. Both subsided quickly with a single Medrol dose pack.

Today I seldom worry about gout. The oxypurinol has worked well and seems to fit in well with the medications being taken for unrelated

conditions. It has not only been highly instrumental in my being able to perform my work and to be self-reliant, but has made a monumental difference in quality of life.

I have been a light aircraft pilot and an organist for many years. Gout made both of these pursuits virtually impossible. I could not manage the communications and navigation equipment in the plane and I lost the ability to safely operate the controls in the aircraft. While serving in the Army in Vietnam I provided volunteer musical service to the various chapel services whenever my duties permitted. I could handle service music, including high mass, while wearing combat boots. Sadly, at the height of the gout flares I could not manage even simple service hymns due to loss of mobility and agility. Since starting on the oxypurinol program I have been able to regain sufficient freedom of movement and again provide volunteer musical services at the church and elsewhere. I suspect my flying days are past.

For very selfish reasons, I wanted to be

able to continue in my profession, as well as to enjoy an improved quality of life. I earnestly hope that oxypurinol makes it to market. I cringe at the thought of losing it, expecting that I might well live out my remaining life as a cripple if the gout returns. I am most appreciative of the folks at Cardiome Pharma for their contribution to my health and that of others. I also appreciate the opportunity to have something to put before the committee. Thank you, Walter J. Clifford.

DR. GIBOFSKY: Thank you, Mr. Mihalo. Our next presentation will be from Mr. Allyn Hamilton. Mr. Hamilton?

MR. HAMILTON: I hate to bore you all again with the crutches, and all that sort of stuff. When I met Dr. Hustetter, who put me on this, he was a new doctor in his arthritic office in Chattanooga, Tennessee. He said, "what are you doing about it?" I told him, I said, "well, I'm drinking a lot of water and I've cut down"--I used to eat liver, calves liver and cooked onions and I could feel my knees swell up while eating this. I

told him I was quitting that. I was drinking a lot of water, keeping my feet elevated, trying to build up my legs because I a golfer. I couldn't even go 18 holes in the golf cart. Now I carry my own bag.

But some of the medicines that we tried, colchicine, allopurinol, Benemid, Indocin which was good for attacks, butazolidin, Clinoril, anturane, cortisone--of course, he would shoot me with cortisone every time he drained the thing, Zyloprim and all my stuff is very dated because I have been on oxypurinol for 20 years and it works like a charm. So, I don't know anything about all these things you all are talking about. I never had to worry about them. But Zyloprim was the medicine of choice for a maintenance drug when I was going through this. The first pill I took, I didn't even get home before I had violent swelling in this shoulder and I think it created an attack. So, I called the doctor back up and he said get back down here. This was a different doctor, of course. I went to about 20 doctors before I finally got on oxypurinol. I went down there and he gave me a

shot of adrenaline and sent me home. He said I don't know what you can do about it, outside of just the normal eating colchicine by the handful, dosing with a bunch of pain pills, with your feet propped up on top of the sofa for days. Just excruciating pain.

Real funny, Dr. Hustetter, when I started with him, he said, "you know, you've got a fantastic threshold for pain." Let me tell you how painful this stuff is, when that pressure builds up it is horrible. Anyhow--let me see, that is pretty much it really. Thank you very much. Cardiome--how do you pronounce it?--is covering my expenses and stuff. Thank you.

Committee Discussion and Questions

DR. GIBOFSKY: Thank you, Mr. Hamilton. That concludes the presentations during the open public hearing. The committee will now begin its consideration of the questions posed to us by the members and staff of the FDA. You have before you a list of questions. There are in eight broad categories with multiple sub-bullets. In the

interest of clarity and efficiency, while many of these issues appear to be inter-related in terms of surrogacy endpoint clinical differences and what patients should be enrolled in trials, I would ask that we consider them in order seriatim rather than kind of go back and forth. So, we will begin with the first question.

Please discuss the utility of serum uric acid as a surrogate marker for the chronic treatment of gout. There are several sub-bullets: If an appropriate surrogate, what level of serum uric acid or amount of change would be considered adequate v of efficacy?

Would an analysis comparing mean change for treatment populations reflect efficacy? Would analysis comparing numbers of individuals in each treatment arm reaching a prespecified level or amount of change adequately reflect efficacy?

Are there advantages to choosing an analysis of either the uric acid levels at last visit or the uric acid levels over time, based on AUC? Does the choice of surrogate as the efficacy

endpoint influence the decision of what is considered acceptable risk?

The question is now open for discussion by the members of the panel. Come, come, don't be shy! Dr. Cush?

DR. CUSH: I think for everyone who practices rheumatology uric acid as a marker for success makes incredible sense. It is, in fact, what we look to do in the management of our patients. But as a sole basis for a drug's approval, withstanding other information, it becomes a little bit difficult. Again, I think we sort of make that leap of faith that if we control uric acid we control the disease but I don't think we have enough really quality data to tell us that control of uric acid leads to better quality of life, less joint destruction, better survival. For attacks, I think there is probably enough evidence to say that, but I think the idea is that it is a large leap that this committee would have to make to back that, and I think to accept that as a surrogate and then require all this other stuff to

show these facts may be passable.

But I think, you know, really there is no reason that a drug in development at this stage can't have one of these surrogates as a primary outcome along with the clinical outcome, and that trials be constructed using both placebo and active controls for extended periods of time to answer these questions.

DR. GIBOFSKY: Dr. Williams?

DR. WILLIAMS: I listened to all this and it certainly isn't one percent of the population. That would be as frequent as rheumatoid arthritis and that is not true in my practice. I think that while I would like to see as an endpoint the decrease in joint destruction and decrease in the number of acute attacks, I think as a practical matter we need to use some sort of surrogate so you can identify the disease by the presentation of crystals. But I think you can use serum uric acid level as a surrogate. We certainly do as we monitor these patients. If we can get it down below 6 we would anticipate that that would

decrease the frequency of attacks and improve the joint function.

DR. CUSH: It goes against the anticipation that that would happen. I think what we have done, we have been holding manufacturers to a higher level of evidence and they need to show us that in truly objective measures.

DR. GIBOFSKY: Dr. Williams?

DR. WILLIAMS: That would be the ideal, but I think that you are going to have trouble getting the number of patients necessary to really get good data to show that you made that kind of change. I hear them saying 6 attacks per year. It is going to take 100 clinics to get 200 patients and those trials are going to be very difficult to do. So, in the meantime I would use it as a surrogate because I think that that is the way we use it now in practice.

DR. GIBOFSKY: To what extent is the serum uric acid a surrogate for total uric acid? We have all seen these pictures of tophi and the tophi can be quite extensive and, yet, the serum uric acid

may be only mildly elevated. So, I guess the question that has been coming up to me again and again is while serum uric acid may be a marker, is it an appropriate marker for total uric acid? Is that what the gold standard should be? Dr. Williams?

DR. WILLIAMS: I think it is a marker of the total serum uric acid. We can lower the serum uric acid faster than we can lower the pool. However, over time if you keep the uric acid low you will gradually lower that pool. Rapid lowering of the serum uric acid may have very little impact on the total pool to start off.

DR. GIBOFSKY: Dr. Cush?

DR. CUSH: Earlier today we heard from Dr. Terkeltaub that measuring total body urate by looking at tophi would make some sense, or maybe even more specialized means. Now we are examining, you know, using a surrogate marker for a disease and its activity, and now we are talking about a laboratory test to look at a disease and its activity. My point is gout is an easy disease.

They hurt. You know, clinical measures work. I think everything else is going to be icing on the cake and I don't see any reason why we can't require strong clinical outcomes. I mean, this is predominantly a disease of pain.

Going to Jim's point, I don't have these people in my clinic either, and over 3600 practicing rheumatologists, we take care of a very small minority of almost 5 million people who have this disease. That means they are out in the private sector. They are being treated by primary carers and emergency room docs, and that is why we don't see them. So, obviously, the trial is not going to be done in my office as well as it is going to be done in a hospital and its emergency room.

DR. GIBOFSKY: Dr. Felson?

DR. FELSON: I actually sketched out the primary endpoints and the pros and cons of each of them. Serum uric acid could be defined in one of three ways as an endpoint, I guess. One is by the regression, sort of continuous measure and does it

change on treatment more than in the comparator. The good news about that is it is powerful because it is continuous. The bad news about that is it may be trivial and be significant.

Then, there is sort of the arrangement that was made for what was called the pivotal trial for oxypurinol, which was at least a 2 mg/dl decrement as the lower bound of the 95 CI of improvement. I actually have a bunch of problems with that. One is that it suddenly dichotomizes the continuous measure and, therefore, makes it less powerful. Another, which I think has been said a few times here, is that I am not sure whether it is clinically important.

Then, the last one would be a reduction to an arbitrary level on the part of a certain number of patients. That is bullet number three, would an analysis comparing the number of individuals in treatment arm reaching a prespecified level or amount of change--we just talked about the prespecified amount of change; this is the prespecified level. The obvious one, based on the

literature and based on the physicochemical solubility of uric acid, sounds like it is less than 6 over a period of time.

That seems to me the only supportable primary efficacy measure that you would use for serum uric acid, if you used one. Now, the problem there is the ability to get to that level would likely depend on the baseline level in a given person or group of people, and it would be harder to reach if some people start off with very high levels. I think one could argue that since there are effective therapies here already, even though not maybe not in some subsets of patients, it might be okay to ask for a high threshold level of proof, which this would be.

Then, the alternative is the Jack Cush alternative. You know, it is interesting, I came here this morning thinking I would choose that. Then as I listened to the serum uric acid discussion I think you guys all convinced me we should go to serum uric acid. Then I think as I thought about what Jack was saying, I think I came

a little bit back towards that because it is such a symptomatic, easily characterizable symptomatic disease and attacks are the central manifestation.

The problems with using clinical attacks are that they increase early in uric lowering therapy so one would have to define it after a certain period of time on treatment or start enumerating them. I think there is another issue in these particular types of patients who would be eligible for these trials. Frankly, I see a lot of these because I practice in a municipal hospital and I am not sure when a given attack begins and ends in any of these patients. They often have very continuously active, smoldering disease and it might be difficult to enumerate attacks in some of these patients.

Then the other thing I think Marc or someone else brought up earlier is that the number of attacks might be affected by co-therapy to prevent attacks. I think you could probably get around that design issue by just requiring constancy of some co-therapy so that it doesn't

vary through the course of the trial. Then you would have an outcome, so you would do number of attacks sort of starting at three months or six months after initiation of therapy per month, or something, and that might work the best of all.

DR. GIBOFSKY: Dr. Hochberg?

DR. HOCHBERG: Dr. Felson is always a hard act to follow because he is so thoughtful in the way he lays things out. I want to step back to the issue of whether uric acid is a surrogate. I guess when I think of a surrogate I think of sort of the evidence-based medicine approach. There is actually a paper that speaks directly to this as to when something is a good surrogate and when it is not a good surrogate. We know from the epidemiological data that measurements of serum uric acid predict the development of gout. So, it is great for that.

We have some observational data, although not from placebo-controlled, randomized trials, that suggest that if you change the measure of uric acid you get an improvement in some of the clinical

outcomes in terms of a decrease in size of tophaceous deposits, as well as a decrease in the number of attacks.

I think putting those two together, you would say, yes, this behaves as a surrogate endpoint. Now, the problem is that the drugs lower serum uric acid so that you are treating hyperuricemia, but the treatment of gout is different because gout is arthritis, and gout is painful and it is clinically characterizable, as Jack, David and others have commented. In a trial which is focused on a drug which would lower serum uric acid the patients are not going to come in naive to treatments for gout. They will either be on colchicine or they will be on NSAIDs or they will be on glucocorticoids. So, they will need to have some background therapy and then one deals with the issue of are you recruiting subjects for a study who have failed previous hyperuricemic therapy in order to determine whether a new agent will lower serum uric acid levels as the primary endpoint, or the secondary endpoint of will it

reduce the number of, let's say, attacks of gout or the severity of arthritis during the course of time in a population that is already being treated for their arthritis.

So, I would look at uric acid as, yes, it is a surrogate marker for gout but it is something which is an appropriate endpoint in and of itself in the patient with recurrent attacks of gout or a chronic gouty arthritis.

DR. GIBOFSKY: Dr. Williams, did you have a comment?

DR. WILLIAMS: As usual, I agree with David Felson but if someone lowered their uric acid by 2 degrees or by 30 percent and they still had a uric acid of 8, I wouldn't find that very satisfactory. So, I would agree that we would have to set a fixed level, and from the data it would appear to be 6 mg/dl.

However, I have one problem with using acute attacks as an endpoint, besides those that have been mentioned, and that is that the disease is so episodic and so unpredictable. So, you are

going to have to follow them for a significant period of time to get enough attacks or enough expected attacks to make a difference. It is not a continuous problem like rheumatoid arthritis and I think that that makes the trial much more difficult and longer and larger to get adequate numbers.

DR. GIBOFSKY: Dr. Cush?

DR. CUSH: Not to be a broken record, but when my patients come back with gout the first question I ask is not what is your acid, I don't even care if I have the lab and the chart, you very easily ask them what has happened since the last time I saw you. The last time I saw you I may have started you on allopurinol or on probenecid or colchicine and loaded prednisone to the mix, and successful therapy is whether you have had attacks or not. Then I feel good about myself when I see that uric acid went down. I don't actually have a target. I mean, I would like them all to be less than 6 but in practice that is not commonly achievable. But what is achievable is control of the disease.

DR. GIBOFSKY: Dr. Hochberg, as you know and as we heard, there is a poor correlation between serum uric acid and gouty attacks. To what extent would that factor into the assessment of lowering serum uric acid as a surrogate marker?

DR. HOCHBERG: Well, I think in terms of the prediction of the development of gout there is actually probably a very good correlation, from the population data at least, for having hyperuricemia and having the subsequent risk of developing gout.

With regard to the individual patient who comes in with acute gout, you know, you are right in that there is a large proportion who will have normal serum uric acid at the time that they present with acute gout. So, I personally think that uric acid has to be looked at separate from the issue of gouty arthritis and go back at least to the way I was taught to practice, which was to treat the arthritis, probably the way Jack Cush treats the arthritis--not too different from the East Coast and Texas--but to focus on the serum uric acid as a measure--and Dr. Terkeltaub can

correct me and maybe tell us how good a measure it is--of total urate pool and the fact that probably reduction in the uric acid will be associated with reduction in the size of tophi, and that needs to be addressed separately.

DR. GIBOFSKY: Dr. Hoffman?

DR. HOFFMAN: I would concur with Marc's observations. While we have all seen patients with normal or borderline uric acid levels come to us with gout, I don't think the issue is so much is there a direct linear relationship between the serum uric acid at any one point in time and will someone get gout. I think it is more of an issue of being supersaturated over time--how long has this patient been building micro tophaceous deposits until the time comes when they actually have what we think of as strip mining of sodium uric crystals from those deposits. If somebody is acutely hyperuricemic, that may not be terribly relevant compared to the person who has been sitting at a uric acid level of 8.5 for 15 years.

But to get more to the bullet point that

we are addressing, is serum uric acid an appropriate surrogate, I think the alternative question is what do we have as a better surrogate? Unless you would like to call on Bob Terkeltaub again to address this, but as far as I know we don't have a means of measuring total body urate pool so we can't use that as a surrogate. And, I am not aware of any other surrogate that is going to serve us better than serum uric acid. A change in uric acid, is it an adequate measure of efficacy? Well, it is one measure of efficacy. I don't think we can use that as the only endpoint in a study. I think we have to use it in conduction with reduction in attacks of gout.

As Jim Williams pointed out, if we are dealing with people who are not having very frequent attacks of gout, that is going to be difficult and going to require a very large number of patients to do that study. So, there are some logistic issues in study design there.

But I think the issue is very complicated because we know it is not just a matter of what

your serum uric acid is or at what point at time, but it is over time and then there are other variables such as crystallization--perhaps there are some that we know of and perhaps more that we don't know of that determine why there are patients whose serum uric acid maybe 10 for 10 years who never get an attack again.

DR. GIBOFSKY: Well, we have heard from the East Coast; we have heard from Texas; we have heard from part of the Heartland. Comments from the West Coast? Dr. Finley?

DR. FINLEY: Mr. Chairman, I share the concern that we do need to have a clinical marker as a surrogate as well as the serum uric acid. As we have heard from the public comments, for the patients, as Jack Cush mentioned, they are not concerned about what their uric acid is. I also share Jim Williams' concerns about us conceiving and recommending to the FDA a study that, you know, for the sponsors is not attainable in a fashion that would be acceptable to the non-rheumatologists who treat most of this disease.

DR. GIBOFSKY: I would hope that the FDA would not allow us to recommend the perfect as the enemy to the good, particularly for patients with gout. How about the Deep South? Dr. Boulware?

DR. BOULWARE: I am actually very comfortable with using serum uric acid as a surrogate marker for this study. I am reading it now more broadly in terms of this broad discussion of a surrogate marker for the treatment of gout. We started off by talking about a very select population and we have boxed ourselves in, saying we probably can't use clinical outcomes of patients because it may be too small or restricted a patient population. But if you really wanted to see if a drug was effective for the chronic treatment of gout and open it to all gout patients, not just those who have intolerance to allopurinol, then we maybe could answer this question. So, I would favor using a clinical outcome marker too, but not if it means that you essentially hamstring the study.

DR. GIBOFSKY: Any other comments from

other colleagues in Baltimore, Dr. Bathon?

DR. BATHON: I would agree that I think a dual kind of outcome is appropriate. I like the idea of serum uric acid but I think it should have a clinical correlate. If I had to choose what outcome of serum uric acid I would like, I think it would be to hold it to the most rigorous expectation, which would be to normalize uric acid and ensure that correlates with reduction in clinical episodes.

DR. GIBOFSKY: Dr. Terkeltaub, your name was invoked for perhaps some clarification of one of Dr. Hoffman's issues. I wonder if I could ask you to address that at this time briefly.

DR. TERKELTAUB: I have some concern that if trials aren't constructed properly, when looking at serum uric acid levels we are going to be impairing development of drugs to treat patients with difficult gout and a high body burden of serum uric acid. The numbers in terms of trying to use serum urate to interpret effects on urate pool size change, if you take a normal man that has a urate

pool of about a gram and that man has 5 L of plasma, then what is in the plasma at a level of 7 mg percent reflects about a third of the total body pool. Whereas, you know, some of the patients that we see with really bad gout have 5, 10, 25, 30 grams of uric acid and then the serum urate reflects really a couple of percent of the total body urate pool.

So, my concern is that when trying to evaluate urate lowering therapies, if we only use serum urate and if we try to pigeonhole people to a level that is considered normal, 6 mg percent, that we are not going to be really looking at people where they have a shrinking tumor burden of tophus and that would be a great mistake.

DR. GIBOFSKY: Dr. Felson?

DR. FELSON: Bob, if the physicochemical solubility is at 7 and we lower it to 6, they have to be, at least at some rate, taking some of that stuff that was out of solution and putting it back into solution and if their kidneys are working, you know, peeing it out or getting it converted to

something else. I mean, it has to be shrinking, doesn't it? Aren't we messing with the dynamic flows of their uric acid pool?

DR. TERKELTAUB: Yes. I think the question is when you have a serum urate level of 10 and you reduce it to 8, are you failing to control the disease? There, I think the serum urate is a problem. You don't get urate crystallization in plasma and serum; you get it in the tissues. And, I don't think serum urate accurately reflects what is going on at the tissue level in that circumstance. You know, if you are reducing the manufacturing of uric acid and you are reducing tissue deposits, which clearly happens in many of our patients who are stabilized on drugs such as allopurinol, then you are not really getting an accurate readout on the serum level.

DR. GIBOFSKY: Thank you, Dr. Terkeltaub. Dr. Geis?

DR. GEIS: I just want to clarify what I think I am hearing. Are you saying if you powered a clinical trial with a primary endpoint being some

measure of uric acid levels, then you would have a manageable sample size to do a trial? And, if you collected clinical outcomes and you weren't powered to see a difference necessarily from placebo but you saw numerical differences, and you were statistically better with uric acid levels, are you then saying you could interpret to mean that drug treats gout? Is that what I am hearing people say? And, if a sponsor replicated that, then you would say, yes, the drug treats gout. It doesn't just treat the uric acid, it treats the gout as long as you had some measure of clinical outcome, although not statistically significant? Is that what I am hearing?

DR. GIBOFSKY: I am not sure we have gone that deep into trial design. We have just been focusing on the utility of serum uric acid as a surrogate marker based on the comments we heard before--

DR. GEIS: Okay.

DR. GIBOFSKY: To what degree a study is powered, or should be powered, perhaps we will get

into with one of the other broader areas. Dr. Williams, you were next with a comment or question.

DR. WILLIAMS: Actually, that addresses exactly what I wanted to say, and that is, when I was referring to an endpoint of less than 6 mg/dl as an endpoint to show that you have efficacy, it doesn't necessarily mean that it would be the total approach that it is an effective treatment for gout. I was trained that if I am trying to lower the serum uric acid pool I would like to get the uric acid to 3 or 4. However, I would not make that the level to demonstrate that you are effective in lowering uric acid.

DR. GIBOFSKY: Dr. Hochberg?

DR. HOCHBERG: I guess before I ask my question, which is really a question to Dr. Terkeltaub, I would comment back to Dr. Geis' question. In one of Dr. Witter's slides on the approved indications for the products that we are discussing, this sort of class, I like the indication that says for the treatment of hyperuricemia associated with gout. I think that

is what we are talking about now because I still consider gout to be a form of arthritis and when I am treating gout I am treating the attack of gout. When I am treating hyperuricemia I am treating hyperuricemia.

So, I would sort of like to know if there are relatively straightforward, reliable methods which are not too expensive to measure the total body burden or total body pool of urate that function better than the serum uric acid level.

DR. GIBOFSKY: A quick replay, Dr. Terkeltaub?

DR. TERKELTAUB: No.

DR. GIBOFSKY: Thank you. That was quick. Dr. Anderson?

DR. ANDERSON: I would just like to comment on the relative power of an outcome as change in uric acid level or reaching a certain level in uric acid versus the clinical outcome of the number of attacks in a time period like a year. Actually, the power for an outcome where you would be comparing two groups for number of attacks per

year is really pretty good. You know, it is fairly reasonable to assume that these attacks follow a Poisson distribution and I think that the study that was proposed by Cardiome is actually overpowered. You know, by the description that is given, it is overpowered for the outcome of cutting the number of attacks by 50 percent. So, really just isn't such a hard thing to do. That is really what I am trying to say.

DR. GIBOFSKY: Dr. Cush?

DR. CUSH: I like the way Marc has divided it up. To make the analogy with rheumatoid arthritis, you know, I treat the arthritis utilization now I am also looking for treatment that would focus on the CRP, treatment that would lower CRP. CRP is a little bit different than uric acid but they are pretty close. CRP is a direct extension of IL-6. Anyway, I have a little bit of a problem with that approach but I think we should get to the real issue which, again, is a surrogate marker, comparing to HIV and bone density and lipids, where there are clear-cut, defined benefits

to control or lessening of those levels. Again, what is the clear-cut evidence for taking a patient who has defined gout--we certainly know that having elevated uric acid levels increases one's risk of having attacks but take it the other way around, they have gout and I presume they have hyperuricemia, what is the evidence that lowering hyperuricemia gives you X benefit as far as quality of life, attacks, extra-articular manifestations, x-ray erosions, damage, disability, blah, blah, blah? I am not aware that there is a lot there. Is there anything there that hasn't been presented today?

So, again, it is a gigantic leap of faith that we are making based on what we have done for years and years and years, which is the problem with the whole gout literature and the research. It has been an empiric disease since Hippocrates.

DR. GIBOFSKY: Dr. Williams?

DR. WILLIAMS: However, in clinical practice if we lower their uric acid we decrease the frequency of their gout attacks.

DR. CUSH: We do?

DR. WILLIAMS: It seems to be so in my practice and we heard from some people here today who have done well on lowering of their uric acid.

DR. CUSH: I don't doubt that but the evidence is what I am concerned about.

DR. WILLIAMS: I agree, we don't have solid evidence.

DR. CUSH: I don't know how I can tell FDA and you, know, draw up a guidance document for this to, you know, leap forward on leaps of faith rather than good evidence.

DR. GIBOFSKY: Are you having a problem with a faith-based initiative?

[Laughter]

DR. CUSH: You are my lawyer, I can't ask you for advice for how to answer that.

DR. WILLIAMS: However, we are not going to have any more new treatments. If we don't move ahead we are going to stay where we have been over the last 30, 40 years.

DR. GIBOFSKY: Ms. McBriar?

MS. MCBRIAR: Yes, I think it is time to do something. There hasn't been anything new for quite a few years and the patients obviously have a need, and we are seeing an increased prevalence and I think we have to choose the best ideas that people have here and move with them and see what we learn.

DR. GIBOFSKY: Dr. Bathon?

DR. BATHON: I agree with what Dr. Cush was saying but I think, drawing the analogy to rheumatoid arthritis again, we learned a lot about the natural history of the disease and the efficacy of a drug that we have been using for a decade or more, called methotrexate, when we did the clinical trials of new TNF antagonists. I think we have that opportunity here. We have to accept the fact that we don't have a lot of data to base our design on right now but if we design the best trial that we can, given the data that we have, we might be able to answer these questions a couple of years down the road and have a better handle on the natural history and the impact of allopurinol, much

less the new drugs.

DR. GIBOFSKY: Dr. Hoffman?

DR. HOFFMAN: I am trying in my own mind to synthesize what we have been hearing from a number of people, and I think what I am hearing, including from Dr. Terkeltaub, is that there are people who clearly have reduced frequency of gouty attacks even if their uric acid is not brought down to some magic number, perhaps 6 or less. We are not sure about how adequate a serum uric acid change of whatever amount you want to choose is in being an absolutely adequate surrogate of efficacy--decreased gouty attacks.

So, if we don't have that degree of certainty, it would appear that the endpoints for a gout study would have to be two-fold. On one level, decreasing serum uric acid and on the other level numbers of gouty attacks per patient over a unit of time. I don't think I could advocate a study that did not include both endpoints.

DR. GIBOFSKY: I think we have had considerable discussion of question I. I would

like to drill down on the five bullets. There will be ample opportunity for further discussion. Our charge was to discuss the utility of serum uric acid as a surrogate marker for the chronic treatment of gout and now perhaps we can just try and get some consensus, without formal vote, on the five bullets. Is there a consensus there is an appropriate surrogate? Is there anyone who would disagree that it is an acceptable surrogate? Not the acceptable surrogate but an acceptable surrogate?

[No response]

Then, what level of serum urate or amount of change in serum uric acid level would be considered adequate evidence of efficacy? Dr. Cush, you had your hand up so I will let you tackle that one.

DR. CUSH: I will reiterate that it is not percentage change, it is absolute value and I will stay with 6 as my target.

DR. GIBOFSKY: Okay. The second bullet, would an analysis comparing the mean change in

serum urate for treatment populations adequately reflect efficacy? Dr. Hochberg?

DR. HOCHBERG: No.

DR. GIBOFSKY: Discussion? Disagreement?

[No response]

Would an analysis comparing the number of individuals in each treatment arm reaching a prespecified level or amount of change adequately reflect efficacy? Dr. Anderson?

DR. ANDERSON: If it was a prespecified level, yes.

DR. GIBOFSKY: Dr. Felson?

DR. FELSON: I didn't understand Jennifer's answer.

DR. ANDERSON: Well, the question was would an analysis comparing the number of individuals in each treatment arm reaching a prespecified level of SUA adequately reflect efficacy? And, I said yes to that, but no if it had been amount of change.

DR. GIBOFSKY: Are there advantages to choosing--I am sorry, Dr. Cush?

DR. CUSH: Going to the prespecified level, I want to get to a point I made earlier, the cholesterol analogy. Cholesterol trials took off because we had drugs to lower cholesterol levels and we thought it was a good idea, and we had prespecified levels we were shooting for. When we did all that we actually didn't know what the long-term benefits would be. That didn't happen until, you know, 50,000 or 100,000 people were treated in long-term trials and we saw reductions in cardiovascular mortality, and what-not. So, there it became a great surrogate. But when it was first used it was probably assumed to be a good surrogate. David?

DR. FELSON: I think, Jack, you made the exact right point earlier when you said we don't know what going to 8 mg means with respect to clinical effect. In cholesterol there were a variety of epidemiologic data that suggested that if you lowered it to a certain amount you would get a lower rate of the endpoint. That is why it was acceptable. The only evidence we have that a

particular level is going to lower the risk of attacks is the level of 6. Since that is what has been studied, that is where we have the evidence. It may well be, as Jim was saying, that if we lower from 10 to 8 we get less attacks but there is no evidence for that. I think it wouldn't be a good idea to suggest that that be the endpoint because it doesn't necessarily have any clinical meaning.

DR. GIBOFSKY: Don't go away from the microphone, Dr. Felson. Are there advantages to choosing an analysis of either the uric acid level at last visit or the uric acid level over time, based on the AUC?

DR. FELSON: There are always advantages in terms of power--well, not always but almost always, to choosing uric acid levels over time because the average one might be a noisy thing. I think the one exception is if the curve shows that on treatment uric acid levels continue to decline, perhaps be dose is going up, then if you pick the very last level you will get the very best reduction. So, I think it depends on the

particular treatment and what the curve of therapy is doing to the uric acid level. I think the other thing is, frankly, increasingly we are interested in effects that have duration. So, I think doing something over time is reasonable.

DR. GIBOFSKY: Let me introduce the last bullet by referring you back to Dr. Villalba's slide 27, entitled, the oxypurinol challenge. Define a population for a favorable risk/benefit--benefit, modest decrease in serum urate; risk, intolerance. With that as background, is the choice of a surrogate as the efficacy endpoint influence the decision of what is considered acceptable risk? Dr. Finley?

DR. FINLEY: The short answer is I think yes. Even though we have been talking about the surrogate as the serum uric acid, you know, in our discussion we talked about who really treats these folks and I think Jack mentioned where the studies will be done, and I still concern myself that as we ask the sponsors to aim for some target, whatever surrogate we pick, and remember who is going to be

doing the studies, and probably not a preponderance of them will be in the hands of rheumatologists necessarily, that choice of surrogate is clearly very important. I would advocate, you know, we consider things beyond the serum urate.

DR. GIBOFSKY: I think we have adequately discussed question I. I would like to move on to question II. There will be much more time for discussion as we go along. We have eight topic areas to consider. So, if we can put up question II, for a drug to be approved for the treatment of hyperuricemia associated with gout, what additional information besides uric acid levels are important to collect? That topic is now open for discussion. I think we have already alluded to some of that. Perhaps we could just have a reiteration in the context of this particular question. Anyone want to tackle that one? Dr. Williams?

DR. WILLIAMS: Well, I think we have discussed that we would like to see some clinical change as well. So, I would like to see both reducing the number of episodes of acute gout plus

decrease in the size of the tophi, two that are mentioned up there.

DR. GIBOFSKY: Certainly, I think we have also commented on renal function in our patients, and to the extent that renal function can cause gouty attacks and to the extent that gout and hyperuricemia can cause decreased renal function, that would be something that would be worth assessing as well. Any other suggestions for information? Dr. Cush?

DR. CUSH: As was mentioned earlier, quality of life and humanistic outcomes I think are important. Obviously, if we are going for this as a surrogate marker we want to see long-term benefits; these are long-term trials. So, joint outcome, disability, work, humanistic function, etc.

DR. GIBOFSKY: Ms. McBriar?

MS. MCBRIAR: I also would like to see quality of life and also perhaps a pain scale, looking at people's pain.

DR. GIBOFSKY: Any other comments? Dr.

Williams?

DR. WILLIAMS: I would just raise a question. Since we talked about radiographic damage, I think most of that is done associated with tophi. I think the damage is a little less predictable maybe than in rheumatoid arthritis. I personally think that we can't have trials that will be long enough to see significant enough changes but I would be interested if others feel differently.

DR. GIBOFSKY: Let me pose a question to Dr. Felson. Given the extensive co-morbidity in patients with gout, to what extent would a disease-specific instrument be preferable to a general instrument measuring quality of life, or to what extent would a general instrument be preferable to the disease-specific instrument, and can you tease out the effect of one co-morbid condition on another, and which instrument should we be looking at in health-related quality of life assessment?

DR. FELSON: No, I think disease-specific instruments are both more sensitive to change and

evaluating the therapy of a given disease and in this situation, where there are so many co-morbidities that are affecting generic quality of life, I think you almost have to use it. I think it is a secondary outcome measure but I think some kind of disease-specific or arthritis-specific measure--I am not sure that HAQ and the AIMS are such bad ideas here, but those would be better.

I think, by the way, it was shocking how many people died of cardiovascular and other things in some of these studies and I am wondering--you know, we are talking about long-term studies here so the attrition rates would be concerning. I think trying to identify eligible patients not just on the basis of their gout or their renal disease but also who don't have class IV congestive heart failure or even class III might not be a bad idea.

DR. GIBOFSKY: Ms. McBriar?

MS. MCBRIAR: I would also like to see a general quality of life because it then can be compared against other diseases and that is always important information.

DR. GIBOFSKY: So, you would want to see both disease specific and general health-related quality of life?

MS. MCBRIAR: Yes.

DR. GIBOFSKY: Dr. Cush?

DR. CUSH: Since we are talking about using a surrogate as a means of approval and looking for other things downstream, I think you have to also then be mindful that this should be a study that really reflects real use, and not use the usual restrictive entry and exclusion criteria but have people who have obesity, and heart failure, and renal insufficiency, and diabetes included here because there are going to be real life issues. You know, as Bob showed earlier about hyperuricemia predicting cardiovascular problems later on, and as David pointed out, I think that is a real concern that one would have to answer by doing these longer-term trials.

DR. GIBOFSKY: Dr. Hochberg?

DR. HOCHBERG: I guess the other issue in following up on this is because of the association

with cardiovascular disease you have a population of people who should be, if they are not already, taking low dose aspirin. One has to consider in the design of the trial the effect of low dose aspirin on urate handling and, if all the patients aren't on it, whether that would need to be stratified in terms of the randomized process as well.

DR. GIBOFSKY: Thank you, Dr. Hochberg. That is category VIII, subsection 3 and I will come back to you and ask for your comments specifically when we get to that point as well. Are we ready to drill down on the three bullets? Any further discussion of the specific question II as to whether additional information is needed to be collected? If not, let's drill down.

Clinical endpoints of a reduced number of gout attacks and decreased size of tophi in trials of uric acid lowering drugs. Dr. Cush, want to tackle that one?

DR. CUSH: I think that reduced number of gout attacks can be done. There are some problems

with defining gout attacks but we probably anguish over it more than we should. Our patients seem to know exactly when they are. My secretary can diagnose over the phone--

[Laughter]

--but decreasing tophi sounds about as intelligent as measuring nodules in rheumatoid arthritis trials. It depends on the person doing the assessments; it depends on the tools you have and using calipers. I think there is a real value in measuring tophi but, you know, it is only a small reflection of total body urate load and maybe we can only see it really well in the elbow and not so well in the feet. As Dr. Terkeltaub mentioned earlier, I think we need newer methods here. Whether it is scintigraphy or labeling or MRI, or what-not, I think that should be done.

DR. GIBOFSKY: I confess I am not sure that there are many of us who actually take calipers to a tophus when we see it.

DR. CUSH: I would be afraid to.

DR. GIBOFSKY: And I can understand why.

But that said, are there or ought there to be preferred methods for measuring tophi? Dr. Mandell?

DR. MANDELL: You can certainly do it with calipers. I think, from a logistics side, that is probably the most cost-effective way to do it. You can certainly follow people who get reduction. But the issue is can you find one that you can actually measure at the same spot under that skin as it moves each time, and I think that is going to be a challenge.

I would like to comment on the gouty attack issue. You know, I didn't say much before about it. I didn't say anything before about the surrogate marker. I am comfortable with targeting uric acid lowering as a marker, but I also think we do have some issue relating to the arthritis, and the design challenge I think is going to be the unique part that when you give this drug, which should decrease long-term attacks, has a very high likelihood of increasing attacks in the short term. That is going to need to be built in and I don't

think we really understand the timing of when that window should be when we should not count that. So, the drug looks worse or better based on the likelihood of getting an attack early and I think that is going to be a real challenge in trial design.

DR. GIBOFSKY: Dr. Hoffman?

DR. HOFFMAN: I think that is a terribly important point but I think it could be circumvented if you started counting attacks perhaps three months after initiation of therapy. But the major heading that we are addressing these issues under are for a drug to be approved. I think at looking at reduction of tophus size would build into a study something that is untenable. We would all like to know it but if you are going to take a year or two or three to see a meaningful change in tophus size at a point where we don't have anything more sophisticated than calipers, then I think that is not feasible to build into these trials. But I can't imagine the trials not taking into account frequency and number of gouty

attacks, perhaps starting three months after drug has been initiated and we, hopefully, have achieved equilibration perhaps also under cover of treatment with a second agent, that is colchicine which is the standard of care.

DR. GIBOFSKY: So let me pose the question under bullet three to you, Dr. Hoffman--I am sorry, there was a question or a comment before? Dr. Bathon?

DR. BATHON: Yes, I think we do a lot of very inaccurate methods of assessment, including joint counts. So, calipers seem even more sensitive to me than perhaps the feel of a finger on a joint.

I want to come back to that point about the early attacks after starting treatment. That is another thing that we learned but are there data that really support the fact that these drugs increase the incidence of attacks? Do we know from the data that before treatment there are X number of attacks and after initiation of gout treatment there is an increase in X number of attacks? I bet

there aren't real data to support that either.

DR. GIBOFSKY: Dr. Felson?

DR. FELSON: I guess, Joan, sometimes there aren't data because it is reasonably clear. I think it is reasonably clear but then, again, I am not usually an anecdotal type guy.

I would like to paraphrase Nancy Reagan with respect to her comment about measuring tophaceous deposits--"just say no." It is going to be very hard to measure reliably. We have many other better measures here, and I think it is also the time it would take to get change is unknown and would be a mess.

There is one question we haven't addressed, which is number of attacks or reduction of attacks. I wanted to try to address that briefly. I think number of attacks is a better choice than reduction in attacks. The reason for that is reduction in number of attacks is contingent upon two things. One is knowing the current number of attacks and the other is knowing how many attacks occurred before this drug was

started, i.e., before the patient experienced the three months worth of potential flares of attacks they might have gotten. So, I think to ask them to remember six months before, or something like that, how many attacks they used to have last year and whether they got a reduced number now is a problem.

The other way to do this would be a very long run-in prior to therapy in which you enumerate the attacks. I don't think that is a good way--I mean, I think a run-in is nice but if we are talking about a six-month run in to get enough attacks to be able to enumerate and follow, I think that is asking a lot of patients. So, I would be inclined to measure or quantify the number of attacks and not try to figure out whether they dropped.

DR. GIBOFSKY: Dr. Hochberg?

DR. HOCHBERG: I would agree once again with David. I would like to throw out a question about another potential measure, and that would be radiographs of the feet to look at the metatarsal phalangeal joint and look at erosions, and possibly

joint space narrowing. You know, we have very good, reliable scales to assess damage to the MTP joints in patients with rheumatoid arthritis, and I am not sure there are any data that have applied these scales to patients with gout but, in fact, that might be something where one could generate such data either as an exploratory outcome in studies or even just for data collection in order to move the field forward.

DR. GIBOFSKY: Marc, are you suggesting that the Sharp score methodology could be applied to a trial of gout treatment agents?

DR. HOCHBERG: Well, I think it would be of interest to see if it could. I guess it is something that Almarack and John Sharp might be interested in doing.

DR. GIBOFSKY: Dr. Cush?

DR. CUSH: It is my understanding Almarack has discussed that but I don't know the details. Sort of to piggyback on what Marc said, fingers and calipers--I agree with David, just say no to tophi, but this may be one situation where ultrasound

might make sense. There are a few centers that do them. Obviously, it would be a select sub-study for any trial but I think that ultrasound could easily identify and quantify tophi over a period of time.

DR. GIBOFSKY: Any other comments on question II? I think we have covered all three bullets. If there are no other comments on question II, please put up question III.

Individuals with gout may demonstrate a broad range of uric acid levels. We have two discussion questions and two specific questions.

Please discuss the range of uric acid levels that would reflect meaningful inclusion or exclusion criteria.

Are there any advantages to recruiting patients with uric acid in a specified range, such as 8-12 mg/dl?

Please discuss whether there is a rationale for studying individuals with values of uric acid over 12 medication/dl.

Is there value in stratifying patients by

uric acid level?

So, first bullet, please discuss the range of uric acid levels--I think we have already touched upon that. Does anyone want to come back and discuss that again? Dr. Williams?

DR. WILLIAMS: Just to address this question in general, I think that to include patients they ought to have hyperuricemia and acute gouty arthritis but I don't know that I would stratify it further.

DR. GIBOFSKY: Dr. Cush?

DR. CUSH: Extremes in uric acid determinations I think bring into play other diseases. So, if we are just talking about gout I don't think we will have these extremes. They will be there but there will be so few of them I think that going after a specific disease indication and characterizing the disease on clinical grounds rather than on uric acid levels I don't think this becomes anything more than a moot point.

DR. GIBOFSKY: Everyone comfortable with that formulation?

[No response]

Are there any advantages to recruiting patients with uric acid in a specified range such as 8-12 mg/dl? Dr. Hochberg?

DR. HOCHBERG: I guess based on what Dr. Terkeltaub has said, I am not sure we can assume the statement that is in the parentheses is correct. Probably based on the data that have been shown to us and that which is in the literature, most patients with gout who would be eligible for a study in which they would receive a hyperuricemic therapy would have uric acid levels above 7 and would fall in the range between 8-12. So, it is likely that with randomization one would achieve some comparability between the groups. I think if one got to the rationale for including people who had levels above 12, they would be less likely to reach the outcome just because they are starting at a much higher level. So, you would probably want to stratify prior to randomization to make sure they were evenly distributed. So, you would stratify patients above 12 and not necessarily

between 8-12--I mean, not necessarily but I don't know enough to inform myself that that is a good thing to do, to stratify between 8-12.

DR. GIBOFSKY: Is the committee comfortable that the parenthetical statement in bullet two is probably not accurate, given what we have heard today, that the serum urate probably does not represent the total body load of uric acid?

[No response]

Any other comments on bullet two or bullet four, which we have kind of alluded to? Anyone else on that or are we comfortable with the comments that have been made? I think Dr. Hochberg also indicated the issues that might be present in patients with values of urate over 12 mg/dl, the possibility of other conditions, but does anyone feel that there might be a rationale for including these individuals in a hyperuricemia related to gout study? Dr. Bathon?

DR. BATHON: I am sort of antagonistic to the idea of setting an upper limit of normal as

long as we exclude cancer patients and that type of thing. I think we want a range of patients with moderate disease and severe disease and we shouldn't exclude those above 12.

DR. GIBOFSKY: Dr. Finley?

DR. FINLEY: I would agree with Dr. Bathon and I would harken back to something that Dr. Hochberg said earlier. We have a growing population of patients who have undergone transplantation and are going to fit this, and the indication I think Marc spoke to was hyperuricemia associated with gout. I have no notion of how big the population might be that would come under scrutiny but certainly would want to know that data, especially when we are talking about rheumatoid arthritis and other diseases that we all treat, longitudinal disease, and perhaps the indications for using these in those settings might be different.

DR. GIBOFSKY: The Chair would have great interest in following the data on uricemia in transplant patients. Dr. Cush?

DR. CUSH: Just to make a statement in favor of over 12 is that that is what the indication is for, uric acid therapy. So, competitors of allopurinol need to compete in that market and those patients should be included and, if need be, if there are enough of them to be sub-analyzed.

DR. GIBOFSKY: Any other comments or discussion on question III? If not, I think we will take one more question before our break. We are running a bit ahead of schedule but we will continue, nonetheless, and take question IV. I think we can deal with question IV relatively easily.

Patients with gout may have renal insufficiency. Patients with renal insufficiency may have gout. Discuss the value of including or excluding such patients in clinical trials. If they are to be included, what range of serum creatinine levels would be important to consider for inclusion? Dr. Boulware, do you want to take a stab at that?

DR. BOULWARE: I think we should include

patients who have renal insufficiency because that will represent a population of patients that we are going to take care of. I am not really clear that establishing serum creatinine levels is as useful as creatinine clearance because that as a surrogate marker of filtration is probably even worse than what we are talking about. So, I don't know what that level should be but I think we should include renal insufficiency.

DR. GIBOFSKY: Is the committee comfortable with the notion of creatinine clearance rather than serum creatinine as the more precise measure of renal status? So, that should be the recommendation? Dr. Cush?

DR. CUSH: More precise although not ideal. Other measures of direct clearance are far better than calculated or measured 24-hour urines for creatinine clearance. There are obviously going to be problems as far as how accurate those are, especially in situations where there is some mild to moderate impairment. It is better than

serum creatinines however. I think that is clear.

DR. GIBOFSKY: Dr. Williams?

DR. WILLIAMS: I agree it is better than serum creatinine but I think as a practical issue it doesn't make a lot of difference.

DR. GIBOFSKY: So, is there a general consensus about including patients with renal insufficiency in these trials as opposed to excluding them? The inclusion is probably, as we have heard, more real world. The exclusion might be more pure but we are aiming for real world. I see nods around the table so we would reaction the inclusion of patients with renal insufficiency. So, what range of creatinine or creatinine clearance would be important to consider for inclusion? How low can we go? Dr. Cush?

DR. CUSH: Or how high in serum creatinine can we go? I think I would exclude patients who have end-stage renal disease and patients on dialysis. That is another can of worms. I am comfortable up to 4 as far as the serum creatinine and maybe as low as 30 cc on a 24-hour creatinine

clearance but, again, I think that I would be more concrete and just make dialysis and end-stage renal disease as a cut-off.

DR. GIBOFSKY: Anyone else? Dr. Felson?

DR. FELSON: Is this a generic set of concerns or is this relevant to just the oxypurinol trials? Because oxypurinol is renally cleared.

DR. GIBOFSKY: I think this is posed as a generic question for incorporation in guidance by the agency in any trial. Is that right, Dr. Harvey? Dr. Witter? They are shaking their heads so it is generic.

DR. CUSH: But David's point is that there needs to be appropriate adjustment for renally cleared drugs.

DR. GIBOFSKY: Right.

DR. FELSON: I think you might be inclined to constrain eligibility for oxypurinol trials with respect to renal insufficiency more than you might for another therapy which is hepatically cleared and where it might not matter so much.

DR. GIBOFSKY: Dr. Mandell?

DR. MANDELL: The other issue though was that your creatinine clearance drops as your ability to use prophylactic therapy to prevent attacks so if that is going to be a primary outcome, that is going to need to be stratified or handled some place along the way.

DR. GIBOFSKY: Dr. Williams?

DR. WILLIAMS: With no more data than Jack has, I would have said 3 as a creatinine.

DR. GIBOFSKY: Okay. You are agreeing with him?

DR. CUSH: Yes.

DR. GIBOFSKY: Then he can't be right!

[Laughter]

Dr. Hoffman?

DR. HOFFMAN: I think trials generically, as we are discussing them, have to include people with renal insufficiency but perhaps not people on dialysis because, again, we are talking about application to real world situations and these are often the people that we are treating. I think while we can include people with varying degrees of

renal insufficiency, we just need to stratify them in looking at outcome efficacy.

DR. GIBOFSKY: Any other comments on the renal issue? Dr. Bathon?

DR. BATHON: I think Dr. Mandell's point is really important. I think all of the medicines that we use for acute attacks can have adverse effects in patients with renal insufficiency and the design of the trial would have to be really careful in terms of spelling out how you could manage acute attacks or how to analyze the data in renal insufficient patients who couldn't get as many ancillary acute management strategies like colchicine and NSAIDs compared to those that could.

DR. GIBOFSKY: Dr. Hochberg?

DR. HOCHBERG: I would just raise the question for discussion, would we want to know or would the sponsor want to know the 24-hour urine uric acid excretion in a subject at entry into a study?

DR. GIBOFSKY: Thoughts on that? Dr. Cush is nodding his head.

DR. CUSH: Obviously it depends on the mechanism of action of the drug, but it seems like a smart thing to do. You know, the drug that we are talking about here we are looking at long-term outcomes over two years or five years and I am not sure that is going to be as important as in a more short-term trial.

DR. GIBOFSKY: Dr. Hochberg, since you posed the question, do you have some feelings on that topic?

DR. HOCHBERG: Well, I was thinking if we are going to suggest that a sponsor collect a 24-hour urine on every participant in order to calculate the creatinine clearance as an estimate of GFR, then you could use that urine to calculate the 24-hour urine uric acid excretion. But it would seem to me that most of the treatments that are being discussed at least, that were discussed this morning and around lunchtime, are focused on decreasing production of the uric acid as opposed to increasing excretion of uric acid. So, I am not sure that it would inform us at all with regard to

the mechanism of action or provide useful information.

DR. GIBOFSKY: Good point. Any further discussion on topic IV? If not, this is a perfect segue, since we are talking about renal insufficiency and urine flow, to take our break and we will resume at exactly 3:02 by that clock for the remaining four questions.

[Brief recess]

DR. GIBOFSKY: Can I ask the panelists and guests to please take their seats so we can begin the second half of the afternoon? Let's resume our discussion with question V, which is a statement followed by a short essay.

Uric acid lowering drugs such as allopurinol are sometimes used at doses higher than those labeled. Discuss the utility of studying multiples, such as twice the higher dose, of the proposed maximum efficacious dose of a new drug. Comment from the panel? Discussion? Dr. Williams, let me impose on you to kick off the discussion, if you would.

DR. WILLIAMS: If we are looking at the efficacy as bringing the uric acid to a specific level, I think the dose that brought the uric acid to that level would be the maximum efficacious dose. I am not sure you need to go higher than that. Since at least the drugs we have right now seem to be relatively--their reaction seems to be idiosyncratic rather than dose related--that you push the dose to that which will bring it down to the level you are searching for, and that would be your maximum dose. You don't need to go higher than that.

DR. GIBOFSKY: Dr. Geis, let me solicit your feelings on this point.

DR. GEIS: I guess would that then raise the question, if the sponsor did that and it worked, that people would say, well, in the real world physicians will keep pushing the dose if we get the patients down to a certain level with a therapeutic and do you, therefore, have efficacy and safety at even higher doses. That is always the struggle I have found that we run into.

DR. GIBOFSKY: So, the suggestion is that a study at higher than the maximum efficacious dose is likely to result in greater use of that greater dose than a study that doesn't study the multiple and efficacious dose.

DR. GEIS: Right.

DR. GIBOFSKY: Dr. Cush?

DR. CUSH: I was confused by your point. Could you say that again?

DR. GIBOFSKY: I am suggesting that hypothetically if there were a study in which more than the maximum efficacious dose were studied and found to be maximally efficacious, or minimally more so, that could lead to greater use of a higher dose than a study which did not study a higher dose, if I understood Dr. Geis. If I didn't, then we will move on to the next question. Any other thoughts on this? Dr. Anderson?

DR. ANDERSON: Do I understand what you are saying as being that whatever is the maximum dose that you study, there will be doctors who will double it in practice, with possibly accompanying

safety issues?

DR. GIBOFSKY: Dr. Cush?

DR. CUSH: That is a natural tendency for all drugs, or a lot of the drugs that we use that are marketed. They come out with a marketed dose with an acceptable toxicity profile and then, once they get to the market, use tends to creep up. Often that is met with some acceptable outcomes, that there isn't much increase in toxicity and there is more efficacy, as in the case of ibuprofen for instance. In the case of methotrexate, we started out with 7.5 mg and now it is a laughable dose. So, time will determine what the real maximally efficacious and acceptably safe drug dose is going to be. Again, I don't know that we can advocate this as a routine part of drug development. I think that it is the responsibility of the FDA to oversee the patient safety and for the manufacturer to get the best possible efficacy while maintaining that safety, and it is up to them to figure out the dose. I don't think we should tell them once you have figured out the dose, now

give us a double dose study. I think that is something that can be done in post-marketing studies by the manufacturer.

DR. GIBOFSKY: Dr. Geis?

DR. GEIS: I guess where I am going with this is that in my experience in other arthrities we would push the dose to show that you got to a plateau, and that by keeping and pushing the dose you didn't get a better, a greater effect. Therefore, it sort of gave the physicians the data that said there is no benefit in keeping on pushing the dose. That is what I am saying here. Would we want to do something like that?

DR. GIBOFSKY: Dr. Mandell?

DR. MANDELL: I am not sure in this setting, where you are talking about an enzyme inhibitor in a heterogeneous population, that you are going to see a maximum efficacious dose. If in a large percentage of your population you increase and increase dose, you still may be lowering the uric acid further. So, I think the maximal efficacious is going to be a difficult thing to

define from early preclinical or Phase 1 trials. moxifloxacin

DR. GIBOFSKY: Good point. Any other comments on this? Dr. Hochberg?

DR. HOCHBERG: I guess part of develop, as Dr. Geis says, is to determine the maximally effective dosage with safety. I think that here, even if it is an enzyme inhibitor, you will have some doses, let's say, at the lower end of the spectrum which may be effective in a certain percentage of subjects but are ineffective in another percentage of the subjects and then you will have to do escalation as part of Phase 2 in order to really find out what the sort of maximal effective and safe dose is in order to get to the top of the range. Because, if you never get to the top of the range, then you are never sure you have the right dose once you go into Phase 3. Then, if you end up getting marketed, what will happen is what Dr. Cush says, you know, the practitioner will end up pushing the dose above that range unless there is evidence that there is clear toxicity

associated with it.

I think another aspect that we have to consider now and that the FDA may want to think about in terms of advising companies is the whole issue of pharmacogenomics and why people don't respond to what might be the maximally effective dose. Maybe they are never going to respond to that agent. This ought to be something that maybe companies should think about studying or collecting data on in order to be able to study it as they bring drugs from development towards the marketplace.

DR. GIBOFSKY: Thank you, Dr. Hochberg. Further comments on question V?

[No response]

I think we will move on to question VI. Please discuss the what could be considered an optimal duration for these trials. Dr. Boulware, may I ask you to begin the discussion?

DR. BOULWARE: This is one of those questions that probably should have had bullets under it because I think it depends on what your

endpoint is going to be. If you want to look just for lowering of serum uric acid you probably could achieve that quicker and, depending on what your endpoint is and where you started from, maybe within 12 weeks. If you want to look at the reduction in the number of attacks, you probably have to go longer and it would depend on what kind of patients you entered into the study and how frequent the attacks were.

Another outcome we didn't discuss earlier but which probably is important is the severity of their attacks. If we maintain the number but reduce severity of attacks and duration of an attack, that may be an important outcome that too and my guess is that is going to take at least six months of a trial.

Finally, if we are looking at reducing tophi size, and we have talked about ways to do that, we saw in earlier presentations a mean of 20 months I think, plus/minus 10 months in order to do that, so that is going to take a long time to do, at least a year to see an effective reduction, but

it depends on the sensitivity of the method you use. With ultrasound maybe you could see a 50 percent reduction in--I don't know--six months.

DR. GIBOFSKY: So, the optimal duration might be different for lowering serum uric acid, for educing size of tophi and for reducing either the incidence or severity of attacks of gout. Is that what you are saying? Dr. Bathon?

DR. BATHON: Yes, but even within one endpoint like reducing serum uric acid it is going to depend on the mechanism of action possibly with the rapidity with which the drug achieves that. So, something that immediately inhibits xanthine oxidase might be relatively quick whereas something that is a uricosuric agent may take longer to have an effect. So, I think it depends on mechanism, the rapidity of the effect of the drug and then, obviously, whether you are doing dose escalation versus starting out with one single dose will make a big impact.

DR. GIBOFSKY: Also depending on concomitant therapies which we will get to in just

a few minutes. Dr. Cush?

DR. CUSH: I like Dr. Boulware's stratification based on the surrogate marker only, which would be a much shorter trial, you know, 24 weeks, as Joan says, depending on surrogate marker plus the primary clinical outcome, which is attacks being longer in 6 months or maybe longer. You could use IC's guidelines for numbers to apply this, you know, 300-600 I guess for a 6-month trial. Then, they are going to have to do the long-term trials if they are going to get the surrogate marker indication and that is going to have to be 2 years, and that is for quality of life, humanistic outcomes, x-ray outcomes, nodular outcomes even, morbidity, mortality stuff. I think real long trials with larger numbers are going to be mandated.

DR. GIBOFSKY: Ms. McBriar, do you think a 20-year period of time is appropriate or too long for assessing changes in health-related quality of life by patient-reported outcomes?

MS. MCBRIAR: I would think at least one

year and see it hold. I think it will be hard on the sponsor but I do think it is important if you want the long-term effect of these drugs to be known.

DR. GIBOFSKY: Other comments on point IV? Dr. Anderson?

DR. ANDERSON: A comment more about the number of attacks, and something that concerns me a little about some of the discussion before about that is that it was suggested that maybe the number of attacks in the first three or six months of the trial could be ignored. But I think it would be better to just keep track of the number of attacks per six-month period and take all of that into account. Depending on the mode of action of the drug, it seems conceivable that one drug might increase them in the first six months and then decrease them after and another one just sort of decrease them slowly. So, that is a feature that one would not want to lose sight of. It isn't strictly speaking on this point.

DR. GIBOFSKY: Any further comments on VI?

Have we adequately discussed this to everyone's satisfaction and provided some input for the staff of the agency to consider?

[No response]

We will move on to VIII, please.

DR. CUSH: Michael and I were just talking about this, you know, over time for quality of life outcome measures this is much more a saw-tooth pattern of disease than even RA because they do spike and the question is if their spikes are infrequent and not that large, then the cumulative hit to the being is going to be less and, therefore, I think a lower duration of follow-up for quality of life outcome is going to be important.

DR. GIBOFSKY: No argument there. Number VII, please discuss the implications of placebo versus active controls and superiority versus non-inferiority designs for clinical trial of uric acid lowering drugs. Is there sufficient data available in the literature to establish a generally accepted response rate for allopurinol--presumably the

appropriate comparator--that could be used for calculating a non-inferiority margin? Dr. Felson, can I ask you to kick off the discussion here, please?

DR. FELSON: Yes, I think we talked a lot about patients who really have no other options where allopurinol has failed them. I think in that situation a placebo-controlled trial is appropriate and a conventional design that is, you know, reject the null hypothesis design, powered appropriately, is also what you probably should be recommending. If these were therapies that were going to be tested as first-line urate lowering agents against allopurinol I think a non-inferiority design would be better. The only circumstance I was thinking about where you could do a non-inferiority design was if you decided--because it sounded like even though the trial we heard about was supposed to be in double failures--what you guys called double failures--in fact, wasn't in double failures; it was in single failures mostly, that is, people who had some kind of trouble with allopurinol and

hadn't actually been rechallenged or desensitized. So, one I guess non-inferiority design one could conjure up which wouldn't be uninteresting would be to test a new agent and compare it to desensitization. So, what you could do is do a randomized trial. You would have to sort of desensitize to placebo, I guess, and that would work. Then, that might be some kind of non-inferiority. I guess that is a non-inferiority design although you don't necessarily know what the response rate for desensitization is. I think it would be better probably initially to do a placebo-controlled trial in people who can't take allopurinol and just deal with it in a conventional design fashion.

DR. GIBOFSKY: Dr. Cush?

DR. CUSH: But, again, we are talking about gout which is sort of maybe the most painful condition that we manage so I really worry about placebo-controlled trials and I don't want to use them unless it is absolutely necessary. But I do think that my education here at the FDA has been

that they like to see a placebo-controlled trial and that might be the perfect instance, to have a small trial for those kind of patients. I don't know how small it would be. If it is 60-120 patients for a limited duration, maybe that is acceptable. But for larger numbers, as you suggested, a head-to-head comparison with allopurinol would make more sense to me using a non-inferiority design.

DR. GIBOFSKY: Dr. Williams?

DR. WILLIAMS: I agree with David. If you are looking at patients who are allopurinol toxic so they can't use it, we don't have another treatment so then I could see a placebo-controlled trial because you are going to use pain relief as your escape. But if you are looking at trying to bring in a new drug, then I would compare it to the standard which is allopurinol.

DR. GIBOFSKY: Along those lines, is there sufficient evidence in the literature to establish a generally accepted response rate for allopurinol that could be used for calculating a non-inferiority margin?

Dr. Hochberg, are you aware of the literature here?

DR. HOCHBERG: No, I am not aware of a generally accepted response rate in terms of the proportion of patients who would have a serum uric acid level below 6 mg/dl with appropriate dosing of allopurinol.

DR. GIBOFSKY: And to the extent that we have been talking about that level as an appropriate surrogate marker, it would be important to have that in the literature.

DR. HOCHBERG: I think so. One of the papers that was referred to by a presenter earlier in justifying that as a level of clinical importance, only about a third of the patients who were in that observational study actually reached that level with treatment.

DR. GIBOFSKY: Any other comments on this point about methodology of superiority versus non-inferiority or placebo versus active control? I think we have established that the answer to the bullet is no, but that doesn't preclude us from

making those suggestions as outlined. Ms. McBriar?

MS. MCBRIAR: I would just want to make sure that the sponsor had decided how to rescue people. This is a pretty serious, potentially damaging disease and it is obviously very painful and I wouldn't want people to be in pain for too long.

DR. GIBOFSKY: I think you are echoing Dr. Cush's concern about placebo trials in such an acutely painful condition. Any other comments on question VII? Dr. Hochberg?

DR. HOCHBERG: Just a comment about the issue of rescue, if the number of recurrent attacks of gout, let's say, is going to be a secondary outcome, presumably in the protocol there would be a standardized method of treatment of those acute attacks when they occur with an agent which, let's say, would not affect serum uric acid levels which presumably would be the primary outcome measure. So, again, if we are going to be looking at agents which are designed to lower serum uric acid levels in patients with gout, then we would anticipate

that those individuals in the study, whether they be in the placebo group or in the active treatment group, are going to have attacks of gout during the course of the study and that they will need to be treated.

DR. GIBOFSKY: Any other comments?

[No response]

Let's move to VIII. Please discuss the implications of concomitant therapies. Can concomitant drugs such as colchicine or non-steroidals be continued during clinical trials for chronic gout? Discuss the implications of permitting or prohibiting the use of concomitant diuretics or low dose aspirin. Is there value in recommending or prohibiting a particular diet? Is it appropriate to restrict alcohol use--presumably in the context of a clinical trial? Please discuss issues concerning the enrollment of patients with kidney stones and inclusion of transplant patients, especially those on drugs such as cyclosporine.

Dr. Hochberg, I threatened earlier to call on you to begin the discussion here so I will

fulfill my promise.

DR. HOCHBERG: Well, these are all important areas and necessary to discuss. I don't want to go at them bullet by bullet but starting with bullet one, definitely, concomitant agents should be continued during the trial. You know, I think as Dr. Cush and others have mentioned here, the hallmark of therapy in patients with recurrent attacks of gout is chronic colchicine therapy in order to prevent recurrent attacks of gout, and we remember that that has sort of come into the armamentarium not from randomized, placebo-controlled trials but from before and after studies. So, obviously colchicine should be continued. There apparently is a sizeable proportion of patients--again, we don't really know what number it is--who are intolerant of colchicine therapy who usually are on chronic NSAID they for prevention of recurrent attacks of gout. So, I think yes, that has to be included. Again, it might be something that one wants to stratify on. You don't want to stratify on too many variables

but you want to make sure that patients that are on them are at least able to continue them in the study, and certainly not washed out.

Do you want me to keep going?

DR. GIBOFSKY: Please.

DR. HOCHBERG: Bullet number two is discuss the implications of concomitant diuretics and low dose aspirin. Well, I guess that depends on the co-morbid condition. Certainly, the population with cardiovascular disease which should be taking low dose aspirin, I think, again, should be in the study. We, again, need to consider the effects of low dose aspirin on renal handling of urate, but since most of the compounds that have been at least discussed earlier today and probably would be in development would be focused on inhibiting xanthine oxidase and production of uric acid, I don't think that is a problem. Maybe diuretics aren't a problem as well in that regard, although if the diuretics are being used for the management of hypertension in clinical practice oftentimes you try and switch agents so that might

be a consideration. But I don't think that I would exclude people who are on diuretic therapy and low dose aspirin.

DR. GIBOFSKY: We will stop there and have further discussion of those two bullets before we go on to the other subheadings. Dr. Williams?

DR. WILLIAMS: I totally agree on bullet number one. Bullet number two, I would think they could continue on their diuretics and low dose aspirin if they had been on them for a month prior to the study and remained constant during the study. I think any impact they had would wash out.

DR. GIBOFSKY: Dr. Bathon?

DR. BATHON: With regard to the first bullet, with NSAIDs and colchicine, I wonder if it wouldn't be a more sensible design to just have a PRN mandate like a week of treatment for each acute attack, or something where you could get them off continuous treatment and just use it for acute management. For renal failure patients where you might not want to be using NSAIDs and colchicine, have a third possibility of using steroids.

DR. GIBOFSKY: Dr. Hoffman?

DR. HOFFMAN: There is an old study--I was discussing with Bob Terkeltaub earlier; I think it probably goes back to the '60s--where people were made normal uricemics who previously had gout and were kept on colchicine, I think it was for six months, or not placed on colchicine and there were some recurrent attacks of gout in both groups between there was clearly a difference of fewer attacks of gout in the patients maintained on colchicine. It is with that in mind that I have always treated patients with colchicine for six months and sometimes even up to a year, realizing that urate stores were going to take a long time to be mobilized. I would be more comfortable with a protocol where, unless there was a contraindication to colchicine or unless colchicine was not tolerated, to have colchicine as the standard of care along with starting a uric acid reducing agent, and to use alternative therapies only if colchicine was contraindicated.

As far as the other points are concerned,

other concomitant therapies including thiazides, I agree with Jim on that. I think that is reasonable clinical practice and should be part of protocols.

DR. GIBOFSKY: Dr. Cush?

DR. CUSH: Prior to this discussion I would have excluded diuretics and low dose aspirin because it would just complicate matters, but certainly you could stratify for those patients and, on further consideration, I think it is actually better to include them because it is common but, more importantly, such patients will be primed to get in trouble; they will be more likely to have hyperuricemia and troubles with that. You know, it is basically selecting for a naturally occurring high risk population and I think we will see more numbers to make judgments as far as the outcomes in efficacy and safety.

DR. GIBOFSKY: Any other comments on bullets one and two? If not, we will move to bullet three, is there value in recommending or prohibiting a particular diet?

At Cornell we have the maxim "when all

else fails, find out what the patient likes to eat and forbid it." I am wondering if that is appropriate in this setting given what we heard from Dr. Terkeltaub earlier. Comments?

DR. CUSH: The point would be to note make the diet an issue. So, you could screen patients if they are taking a particular diet, but I think any diet restrictions should not be a part of the clinical trial. I think you want to take a population that does not have a dietary restriction going in. That would be my guidance.

DR. GIBOFSKY: Other comments on this? Dr. Felson?

DR. FELSON: I think this and the next one we can knock of probably at the same time. They are both similar issues. Maybe alcohol is part of the diet, maybe it is not. I think this is probably a good clinical practice issue. I would be inclined to let people know what the issues are about diet and just proscribe dramatic changes in diet. You know, if you are part of this trial, we would like you not to adopt the Atkins diet in the

middle of it because that might affect your uric acid and we might not be able to evaluate the therapy we are trying to evaluate.

With alcohol, I think I would be inclined to do more or less the same, with the exception of trying to exclude, as we often do, patients who tend to use excessively in part because that is going to be very difficult for you to deal with for uric acid levels and in part because they are likely to be non-compliant and would introduce a variety of other considerations and concerns.

DR. GIBOFSKY: Ms. McBriar, could I ask you to comment on the feasibility of instituting these kinds of life style or social habit changes in patients with chronic disease?

MS. MCBRIAR: I think it is probably one of the harder pieces to do. I think it is important and I think it is part of the overall care for patients and that should be a message that we all get out, but I think if we are trying to study the drug we are right not to throw too many different things into it that might complicate the

answer.

DR. GIBOFSKY: Any further discussion on those two bullets?

[No response]

Let's go on. Discuss issues concerning the enrollment of patients with kidney stones. Dr. Boulware, your thoughts on that?

DR. BOULWARE: I guess I have always thought of renal stones as being part of the whole spectrum of gout so I would not think you would want to restrict them but include them in there. I guess it would require a separate stratification for looking at success of treating stones and recurrent stones, but we are all rheumatologists treating gout and arthritis attacks separately too. But I would think you would want to include them.

DR. GIBOFSKY: Any other comments? Dr. Finley?

DR. FINLEY: The question is phrased as kidney stones generically. Is there a feeling--I don't know, I thought it was in the slides that there is an indication for this not only with uric

acid stones but calcium oxalate stones as well. Would that have to be teased apart, or would there be a recommendation to the sponsor, or would the FDA be interested in defining what the stone is, what the makeup of the stone is?

DR. GIBOFSKY: I suspect we would learn that not all of our patients are as compulsive and diligent as our colleague who came to us with his stones for us to analyze, if need be. But the question is should we stratify patients with or without nephrolithiasis in a study looking at reduction of serum urate as a surrogate marker for gout. That is the question on the table. Anyone else want to comment on that? Dr. Felson?

DR. FELSON: I think you let your patients in. I think it becomes an interesting sub-study to evaluate the effect of lowering uric acid on that outcome, and I would hope that the sponsor, whichever sponsor this would be for the studies, would be inclined to fund that part of the sub-study, which wouldn't be all that difficult to do. It would be real interesting information.

DR. GIBOFSKY: Dr. Williams?

DR. WILLIAMS: I agree. I think it would be interesting. I doubt you would have enough power to make any decisions.

DR. GIBOFSKY: Dr. Hoffman?

DR. HOFFMAN: The type of stones becomes something of a complicated issue because even people who wind up having uric nephropathy--if I am not mistaken and Bob Terkeltaub may want to comment--often have calcium oxalate stones because the initial crystallization is with urate on top of which calcium oxalate is laid down.

DR. GIBOFSKY: Other comments on bullet five? Dr. Hochberg?

DR. HOCHBERG: While I agree that people with stones and hyperuricemia could be entered into the studies that we have been discussing, they also could serve as the population of a completely separate study which I think would be relatively easy to recruit from urologists who see patients with recurrent stones and I am sure measure or at least could be convinced to measure serum uric acid

levels. Allopurinol, if I remember correctly, is the standard of care for patients with recurrent stones with any etiology because of the point brought up by Dr. Hoffman. So, people who are intolerant of allopurinol would be candidates for hyperuricemia therapy if they have hyperuricemia and recurrent stones.

DR. GIBOFSKY: Everyone comfortable with our discussion of bullet five? Any further comment? If not, let's go on to bullet six, please discuss inclusion of heart and/or renal transplant patients, especially those on drugs such as cyclosporine.

I think we heard from Dr. Terkeltaub this morning that cyclosporine is going to be a footnote to the gout story but, nevertheless, there are many patients still on it. How does the committee feel about offering input into the inclusion or exclusion of these patients, who are receiving transplants whether or not they are on cyclosporine, for these kinds of studies? Dr. Cush?

DR. CUSH: I would exclude. I think it is a problem for the transplant world. It is a relatively small problem compared to the numbers we are talking about in the issues above that, where we are trying to include real-world patients. So, I think that is a second study or post-marketing study that has true value, but I am not sure it is necessary for registration.

DR. GIBOFSKY: Are you suggesting that renal transplant patients don't exist in the real world, Dr. Cush?

DR. CUSH: Not in my real world.

DR. GIBOFSKY: They do in mine, Dr. Cush.

DR. CUSH: Oh, really!

DR. GIBOFSKY: Any other comments? It is a small subset of patients, granted.

DR. WILLIAMS: I would just agree that I think studying cyclosporine and uric acid is a separate study.

DR. GIBOFSKY: Dr. Hoffman, did you want to comment?

DR. HOFFMAN: I think it is in a sense a

separate study but if someone is looking at a new agent, this is a group of people I think have fairly serious problems when they do get gout and they do need to be studied. I would lean more towards including them as a subset for separate analysis.

DR. GIBOFSKY: Dr. Finley?

DR. FINLEY: Dr. Calabrese showed a couple of patients and I think of the one patient that I took care and his gout predated his transplantation, and once he got transplanted and was on cyclosporine his gout was immeasurably more difficult to care for. I don't know that this is a subtext for how we are discussing this but the notion that there weren't individuals who were gout patients predating their transplantation ought to be thought of as we flavor this discussion. I concern myself with those real-world patients. Transplants used to be uncommon; used to be not part of our practices. Now we see patients who commonly have those.

DR. GIBOFSKY: Dr. Bathon?

DR. BATHON: I think the issue with oxypurinol might be different from other drugs that we might consider down the road. In general, a brand-new drug that has not been tested in people is probably not a drug that you would want to put into patients who have a renal transplant initially. So, I would think they would be a later, separate study for most brand-new drugs that are being evaluated.

DR. GIBOFSKY: Any other discussion on bullet six? Dr. Hochberg?

DR. HOCHBERG: I would agree that patients post-transplant should represent a separate population for studies. Another consideration is also because of the adverse events which would be much higher in the population because of the co-therapy, the potential risk of infection, etc. which would be difficult to interpret if post-transplant patients are intermingled with patients who have primary gout in a large population and may not be evenly distributed.

DR. GIBOFSKY: Any other comments?

[No response]

I think we have adequately discussed all of the materials presented to us in appropriate depth and detail. However, are there any issues that we either haven't discussed that any of the members of the panel would like to bring up, or any of the bullets that we have discussed that any members of the panel would like to made additional comments on or go back to for further discussion? Dr. Geis?

DR. GEIS: Would it be useful to just talk for a few minutes about the definition or identification of patients with chronic gout? Because if we don't have that right in the inclusion-exclusion criteria we will be in trouble regardless of what we measure.

DR. GIBOFSKY: The question for us is the issue of a definition of chronic gout. Do we want to offer some suggestions as to what the term "chronic" should mean in this setting? I think we have considered frequency of attacks. We had a brief discussion on severity of attacks. But do we

want to offer a little bit more guidance? Dr. Felson?

DR. FELSON: I actually wanted to bring up a different issue but it is not unrelated to Dr. Geis'. I think it would be reasonable, since we are talking about therapy for people who can't take allopurinol but for whom allopurinol would otherwise be indicated, to use the same definition that is published and accepted for allopurinol use. I think Bob Terkeltaub went over it earlier today and I am not sure I remember all the details, but it is a particular uric acid level, but I think you need three attacks per year as sort of the criteria that are out there. That would seem like the right thing to do, with some kind of good documentation that there have been attacks.

What I wanted to raise, I have sort of been thinking about how one would evaluate subjects in trials or participants in trials and it wasn't clear to me how you would get the number of attacks. Would you see a patient every three months and say how many attacks have you had since

we last saw you? Or, do you have them come to see you with every attack, creating some chaos in your practice, so you can document those attacks?

I am also mindful of the fact that we are involved in an Internet study where we are finding that people actually have attacks much more often than they necessarily see doctors with. So, I am not sure exactly what the answer to that question is, but I think it is something worth discussing and considering. If serum uric acid is a primary outcome, then that is easy. You can just have them come every three months and get a serum uric acid. But if it is number of attacks in the interim, then if you have them come every six months or three months and ask them to remember, their memory may not be all that accurate. You may want them to come in with every attack if you want to have a document or attack list. So, I don't know exactly how that would occur.

DR. GIBOFSKY: Dr. Cush?

DR. CUSH: Tomorrow I was going to make the proposal about what is an acute attack. I have

not read a really good definition of that but I think we were all taught it in medical school, using gout as an example of the four cardinal signs of inflammation--redness, warmth, pain and swelling--and that an acute attack could be three our of four, two out of four. Hence, the ideal situation would be that as defined by a healthcare provider on direct examination, although it might be interesting to also ascertain whether patients could make the same judgment using the same rules.

I think we are all impressed that patients who have gout often do return to the clinic and say, "well, I had an attack last month" or "I've had five attacks since I last saw you," but they have no joint swelling and you find out it was just that they had a little more pain in the instep. They just jump on it with prednisone or colchicine or something. You are not sure if it was a true attack but they define it as an attack. It is certainly not like those first few attacks where they couldn't walk and they were on crutches, and they were in the emergency room and the sheet was

bothering me--you know, the classic gouty thing. I think sticking to the four cardinal signs of inflammation as a measure of attacks makes most sense.

DR. GIBOFSKY: Dr. Cush, how would you deal with or how do you deal with the frequent coexistence of gout with pseudo-gout in terms of defining what the etiology of the inflammation was?

DR. CUSH: Well, I think it depends on the nature of the therapy that is used to treat that individual. You could discount the fact that they could exist together, as could septic arthritis be in the mix there as well. I think if my therapy wasn't working when it should be, that is when I start the existence of another background condition such as pseudo-gout. But talking about uric acid lowering therapies, theoretically they should not be effective in preventing attacks, whereas colchicine and non-steroidals and steroids would certainly have effect on both conditions.

DR. GIBOFSKY: But the question implicit in Dr. Felson's statement is what would the gold

standard be for identifying those attacks. Should it be the physician observation, the patient self-report? If it is the physician observation, should there be a demonstration of uric acid crystals in the fluid each time?

DR. CUSH: No, my suggestion is that it should be by direct examination by a physician or someone in the trial to assess the patients on a PRN basis as it arises. I don't think crystal identification is necessary. Again, I threw out that maybe patients could ascertain this having some very defined rules about what a true attack was, but that would be a study for someone to do to show patient-derived variables compared to physician-derived variables, hopefully, with the idea of coming away with easier ways of doing long-term trials in the future.

DR. GIBOFSKY: Dr. Williams, you have a comment?

DR. WILLIAMS: Jack covered much of it but I am a little concerned about self-reported attacks of gout because I have gout patients who tell me

they had an attack that lasted several hours or a day and without treatment went away, and I suspect those really weren't attacks of out. I think if you are going to use that as one of your measures you have to have them evaluated by an investigator.

DR. GIBOFSKY: Any other comments from members of the panel regarding the information we have covered today, or any other topics you would like to raise in this context? Dr. Hochberg?

DR. HOCHBERG: Well, just for completeness sake in this context I guess, there is the push and pull here. While it would be nice to have subjects who would call in to the study nurse, let's say, at the time that they are having an attack of gout so they could be seen in order to have a health professional concur that this is, in fact, an attack of gout, that may impact on recruitment and retention, particularly for a study where if you are looking for people who are intolerant of allopurinol, let's say, they may be widely dispersed; they may not live necessarily close to the individual physician. Or, if we are going to

recruit in general from a large population in the VA healthcare system we may have problems getting those individuals in.

So, there are validated criteria which have been published for survey purposes to validate a diagnosis of acute gout by the American Rheumatism Association, now the American College of Rheumatology. So, sponsors may want to think about using those in conjunction with some type of telephone monitoring on a frequent interval in order to eliminate the problem of recall over three months between visits, let's say, with monthly telephone monitoring--"have you had an attack of gout in the past month?" If the answer is yes, try and collect some information about it. If not, "thank you very much. We'll call you in another month and we'll see you for your uric serum acid monitoring visit in three months."

DR. GIBOFSKY: Any further discussion or comment? If not, let me thank you all for your participation. Dr. Witter, Dr. Harvey, did you get the input that you were looking for from the group?

Dr. Harvey, any concluding remarks?

DR. HARVEY: I think that there has been a lively and a thoughtful discussion on all of the topics by the committee, and I think there is a lot here for FDA to think about and I would like to thank the committee for all of your work and especially thank the Chairman today. Thank you.

DR. GIBOFSKY: Thank you all very much for your input and hard work and making my role here particularly easy. Tomorrow morning we will begin at 8:00 sharp. Please bring your luggage with you if you are staying at the hotel. It will be stored here in the FDA offices, and we will depart from here tomorrow evening to our respective homes or wherever else we are sojourning. The hotel shuttle should be here momentarily to take those of us who are staying at the DoubleTree back there. This concludes the formal part of the meeting. I will see you all tomorrow morning.

[Whereupon, at 4:50 p.m., the proceedings were recessed until 8:00 a.m., Thursday, June 3, 2004.]