DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE

DAY II

Thursday, June 3, 2004

8:04 a.m.

ACS Conference Room
Room 1006
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

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

Members

Jennifer 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 (SGE) Consultants (Voting)

Bruce N. Cronstein, M.D.
Brian F. Mandell, M.D., Ph.D.
Michael H. Weisman, M.D.
H. James Williams, M.D.

Government Employee Participants/Discussants (Voting)

Marc C. Hochberg, M.D., MPH
Robert Terkeltaub, M.D.

FDA

Brian Harvey, M.D., Ph.D.
Joel Schiffenbauer, M.D.
Sharon Hertz, M.D.

C O N T E N T S

Issue: Trial Design and Endpoints
for Drugs for Acute Gout

P R O C E E D I N G S

Call to Order

DR. GIBOFSKY: Good morning. I would like to welcome everyone on the panel, as newly constituted, together with the members of the audience, to the Arthritis Advisory Committee hearing. This is the second day of our meetings on a very interesting topic, Chronic, and today, Acute Gout.

My name is Allan Gibofsky, and I will be chairing the meeting today. I would like to begin by asking the members of the panel, as reconstituted, to please introduce themselves beginning on my right.

Introductions

DR. GEIS: I am Steve Geis. I am the representative from the pharmaceutical industry. I spent 18 years doing clinical research in that industry.

DR. FINLEY: Michael Finley. I am Associate Professor of Medicine at Western University College of Osteopathic Medicine of the

Pacific in Pomona, California, and I am a rheumatologist.

DR. CUSH: Jack Cush, Presbyterian Hospital of Dallas. I am a rheumatologist.

MS. McBRIAR: Wendy McBriar, Director of Arthritis Services, Virtua Health, in New Jersey. I am a nurse and health educator. I am the Consumer Rep.

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

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

DR. MANDELL: Brian Mandell, Department of Rheumatology, Cleveland Clinic, Cleveland.

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

MS. PETERSON: I am Jayne Peterson. I am the Acting Executive Secretary for the meeting today.

DR. GIBOFSKY: Allan Gibofsky, Professor

of Medicine and Public Health at Weill Medical College of Cornell University, a rheumatologist.

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

DR. HOFFMAN: Gary Hoffman, Professor of Medicine and Chair of Rheumatology at the Cleveland Clinic, rheumatologist.

DR. HOCHBERG: Marc Hochberg, rheumatologist, Maryland Veterans Affairs Health Care System, and Professor of Medicine at the University of Maryland School of Medicine, Baltimore.

DR. WEISMAN: Michael Weisman, Chief, Division of Rheumatology, Cedars-Sinai Medical Center, Professor of Medicine at UCLA.

DR. TERKELTAUB: Robert Terkeltaub, VA Medical Center, San Diego, UCSD, rheumatologist.

DR. CRONSTEIN: I am Bruce Cronstein, New York University School of Medicine. I am Professor of Medicine, Pathology, and Pharmacology.

DR. SCHIFFENBAUER: Joel Schiffenbauer,

FDA, Division of Analgesic, Anti-inflammatory, and Ophthalmic Drug Products.

DR. HARVEY: Brian Harvey, the Deputy Office Director and currently Acting Division Director, and I am not a rheumatologist.

DR. HERTZ: Sharon Hertz, Deputy Division Director for the hosting division.

DR. GIBOFSKY: Thank you. I would like to begin by apologizing to the committee and to the audience, I did promise a prompt 8 o'clock start today, however, we were subject to the vagaries of Murphy's Law in getting here. As everyone on the committee knows, rheumatologists and non-rheumatologists included, Murphy was indeed an optimist.

A couple of housekeeping announcement. The committee, by consensus, has decided to shorten its lunch from an hour and a half to only half an hour, so as to have more time, if necessary, for deliberation.

As a result, the public hearing will begin one half-hour after the conclusion of the morning

session, which may be close to the 1 o'clock time, but may be somewhat before it. If there are any individuals here who would like to be heard during the open public hearing, please schedule that with the Acting Executive Secretary or another member of staff, so that we can queue them in, in an appropriate and timely fashion.

With that, I would like to turn the meeting over to Dr. Harvey for some opening remarks, but before that, Ms. Peterson will read the Conflict of Interest Statement.

Conflict of Interest Statement

MS. PETERSON: Thank you. 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 the 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. Michael Weisman has been granted a waiver under 18 U.S.C. Section 208(b)(3) for consulting with a competitor on a matter unrelated to the topics to be discussed at this meeting. He receives less than $10,001 a year.

Dr. Bruce Cronstein has been granted a waiver under 208(b)(3) for serving on a speakers bureau for the sponsor of Arcoxia. He speaks on topics unrelated to those being discussed today, and receives more than $10,000 a year.

Dr. H. James Williams has been granted a 208(b)(3) waiver for serving on a speakers bureau for the sponsor of Arcoxia. He speaks on unrelated topics and receives from $5,001 to $10,000 a year.

Dr. J. Michael Finley has been granted a 208(b)(3) waiver for serving on a speakers bureau for the sponsor of Arcoxia. He lectures on unrelated topics and receives more than $10,001 a year.

Dr. Marc Hochberg has been granted a

208(b)(1) waiver for serving as a consultant and speaker for the sponsor of Arcoxia. He consults on unrelated issues and receives less than $10,001 a year. His speaking is sometimes related to the use of products in gout. He receives from $5,001 to $10,000 a year for speaking.

Dr. Robert Terkeltaub has been granted a 208(b)(1) waiver for speaking for the sponsor of Arcoxia in gout. He receives less than $5,001 a year.

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

Lastly, we would like to also 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 products they may wish to comment upon.

Thank you.

DR. GIBOFSKY: Thank you, Ms. Peterson.

Now, Dr. Brian Harvey, Acting Director of DAAODP of the Food and Drug Administration.

Dr. Harvey.

Welcome

DR. HARVEY: Good morning. Thank you once again. I wanted to thank the Committee again for their services today. Yesterday's discussion was very lively and enlightening, and certainly what we all were looking for today. Of course, we will be talking about treatments for acute gout, and we are looking forward once again to a lively and thoughtful discussion.

I would also like to thank, looking ahead to the public speakers this afternoon and also to our partners in industry who will be presenting today, today we will be talking about clinical trial designs for future clinical trials, as well as what might currently be underway.

It is a general discussion that is going to help FDA and our industry partners to sort of chart future directions in treatments for gout.

So, with that, we actually will get started and move on since we are on a fairly tight schedule, and at this point I would like to introduce Dr. Joel Schiffenbauer, who is a senior medical officer here in the Division, for his presentation Gout: Clinical Review and Trial Design Issues.

Gout: Clinical Review and Trial Design Issues

DR. SCHIFFENBAUER: Good morning. My topic for discussion this morning is Gout: Clinical Review and Trial Design Issues. My presentation will highlight issues for the Committee to consider in the design of trials to study the treatment of

acute gout.

Gout is caused by a deposition of monosodium urate crystals around and in the tissues of the joint. As was discussed yesterday, there are three distinct stages: asymptomatic hyperuricemia, followed by acute intermittent gout, which is the focus of this morning's discussion, and then subsequently, chronic tophaceous gout.

The initial episode of gout usually follows decades of asymptomatic hyperuricemia. It is characterized by intense pain and inflammation, and this is an important point to consider in determining the endpoints to study in any trial of acute gout.

It usually begins as a monoarticular involvement most often with the first metatarsal phalangeal joint.

The natural course varies with improvement and resolution in days to one to two weeks, and this a second important point to consider from two aspects of the trial design.

First, it will help determine how long the

duration of trial should be in acute gout, and, secondly, whether we consider using superiority or non-inferiority designs, and I will come back to this is a few slides.

During the intercritical periods, joints are virtually free of symptoms although crystals may be found.

This is an example of what we are dealing with. This individual has swelling, redness at both the ankle and the first MTP joint, and will likely have extreme pain in both of those areas.

This is the inciting agent, the uric acid crystal, which in this photomicrograph, is found within a white blood cell.

Standard approaches to therapy are summarized in this slide, and you will hear more about this in detail from Dr. Cush following my presentation, but there are several approaches to therapy, and those include nonsteroidals of which there are several that are approved for us in acute gout, colchicine, which is approved for both oral and intravenous use, as well as glucocorticoids,

which are approved, and ACTH, which has been used frequently, but is not approved for use in acute gout.

The remainder of the presentation will focus on specific trial design considerations, but before I get to that, there is some general trial design information that is available at the FDA web site for individuals in the community to search.

The E9 and E10 documents, which cover statistical principles and choice of control groups in general trial design, and then specifically, two guidances in rheumatoid arthritis and osteoarthritis.

In addition, there are the CONSORT recommendations which were mainly geared towards reporting of clinical trials, but in which there is useful clinical trial design information available, and I have provided the reference for that.

So, focusing now on acute gout. Gout is a unique medical disorder that deserves specific studies and its own labeled indication or is a model of acute pain. We would ask the Committee to

discuss this as one of their initial questions, because this discussion will influence what outcomes we wish to look at in any trial of acute gout.

The first consideration is who do we recruit into these trials, what are the inclusion and exclusion criteria. First, is documentation of crystals critical? Should this be at the time of flare, that is, when the patient presents to be entered into the trial, or any previous documentation, if they have had a joint tap within a year or two, is that adequate?

If they have had crystals documented from the knee, but now they present with an ankle that is swollen, would that be acceptable?

Or are clinical criteria sufficient to serve as entry criteria? For example, the ACR classification of acute gouty arthritis in which 6 of 12 clinical, laboratory, and x-ray criteria may be utilized. I have listed some of those criteria on the next slide.

For example, more than one attack of acute

arthritis, maximal inflammation developed within one day, attack of monoarticular arthritis, first MTP joint pain or swelling, suspected tophus, or hyperuricemia, and there are additional clinical criteria, and we would ask the Committee to consider what the diagnostic criteria should be.

Let me turn now to the second consideration, and that is whether the trial should be a superiority or non-inferiority trial. Superiority to placebo is preferable as this is the most straightforward way of demonstrating efficacy, but the question remains are placebo-controlled trials in acute gout ethical.

This question arises because of the severity of pain in acute gout, however, I would like to point out one interesting fact. If one examines baseline VAS pain scores from trials in acute gout, and compares those to baseline VAS scores in trials in acute pain, such as postoperative trials that we see at the Agency, there is, in fact, very little difference in the baseline VAS pain scores. In trials for

postoperative pain, we allow placebo controls to be performed.

Now, the question remains, is a baseline VAS pain score of 50 in a gout trial, the same as a 50 in a postoperative knee replacement or hip replacement. I think that is a question that can't be answered right now, but nevertheless, the baseline pain scores seem to be very similar.

One approach to consider to incorporate placebo would be examining the use of rescue or time to treatment failure as a primary outcome. This early escape design reduces exposure to suboptimal therapy and may be acceptable to incorporate placebo.

There are, however, several alternatives to placebo-controlled trials, which I have listed here. The first is a trial with an active comparator with a demonstration of superiority of the new drug to active comparator.

This might be a very acceptable approach especially if we are interested in better and more efficacious drugs.

The second approach could be a dose-controlled study. By this, I mean a study where we examine several dose levels of the drug, and we demonstrate superiority of the high dose of that drug to the low dose. Again, this would allow us not to incorporate placebo.

Lastly, is the active comparator and non-inferiority design.

If the non-inferiority design is chosen, the question is which comparator would we want to compare if the new drug is a nonsteroidal, would we want to compare a nonsteroidal comparator, or would we allow a drug, such as colchicine, to be the comparator in a nonsteroidal trial, and if so, what is the non-inferiority margin.

Are there historical adequately controlled trials, and by that, I mean placebo-controlled trials, that are of similar design to support the non-inferiority studies? Indeed, if you look in the literature, there is only one true placebo-controlled trial comparing the efficacy of colchicine to placebo, and there are no

placebo-controlled trials looking at nonsteroidals.

If no placebo is chosen and non-inferiority design is considered, the issue is always of sensitivity of the trial, that is, do we know that both drugs work, or is it possible that both drugs do not work.

In fact, since gout is a disorder in which pain resolves spontaneously, this may have implications on the choice and duration of the trial using an non-inferiority design, and we would like the Committee to consider this in their discussions.

There are a number of domains that can be examined in a gout trial. Certainly, pain I think is a critically important domain, but there are several others that can be examined, and those include inflammation, some measure of function whether it be walking, ability to walk, ability to work, or some other function, patient or physician global assessment of disease and/or treatment, and then possibly some health-related quality of life measure, although in a trial of short duration,

this may not be as critical.

Let me turn now to some of the primary outcomes or some of the outcomes to discuss.

The first question is: What is the value of reduction in pain as the primary outcome? If this is considered one of the primary outcomes, then, we would anticipate measuring some of the typical parameters that we measure in an acute analgesia trial, and these include pain intensity difference, pain relief, time to onset, time to re-medication, multi-dose efficacy.

The second question is: Is there value in additional endpoints beyond pain? If we feel that gout is a unique clinical entity, and is characterized by both pain and inflammation, then, should we include inflammation as part of the outcomes that are measured.

However, measurements of inflammation may be difficult to standardize, and this should be considered by the Committee.

There are some additional outcomes I would like to suggest that may, in fact, allow us to

capture the totality of the treatment experience. For example, rescue, that I have already mentioned, time to rescue could be one outcome, or the number of individuals using rescue in a predefined period of time, such as 24, 48 hours, or some other specific time.

Alternatively, time to complete resolution would be a possible outcome, or time to 80 percent or 50 percent resolution, and then lastly, a form of a responder index, such as the number of subjects with good to excellent pain relief in some prespecified period of time.

This raises the next question: What should that time be, when should we seek to measure response to therapy?

Again, if, as we all agree, that pain is a hallmark of this disorder, and we would certainly like to see patients improve within a relatively short period of time, but can we ask for a response within a hour, should it be within the first 8 hours, within the first 24 hours?

I would remind you also that gout will

tend to improve spontaneously over a relatively short period of time, and this may have impact on something, such as a time-weighted average, or should we consider a combination.

We would certainly want to capture some efficacy measure early in the course of the treatment, as well as possibly later in the course of the treatment over a few days. We would ask you to try and consider this in your deliberations.

There are several additional trial design considerations that I would like to put forth.

Is there value in stratification by the following: renal function, uric acid level--these probably in a short-term trial will not be critical--or by tophi, or by the number of joints involved, such as polyarticular or monoarticular arthritis.

If we consider the inclusion of individuals with polyarticular arthritis, it may be important to identify a signal joint, but then the concern is how do we evaluate the totality of the response in other joints.

How should we deal with concomitant medications, other nonsteroidals, other pain medications? Should we allow pain medications to be included during the efficacy trial, so as to keep individuals in the trial and reduce the dropout, and therefore, imputation of missing data?

How do we handle low-dose aspirin, diuretics, or other drugs that may influence the renal clearance of uric acid? Again, in a short-term trial, these may not be critical issues, but we would ask the Committee to consider this, and then diet and alcohol intake, the same concerns.

Some additional considerations. I have already alluded to the evaluation of single and multiple dose efficacy. This is analogous to the requirements that we have for studying an acute analgesic. We would like to know how the individual fares within the first few hours of therapy, as well as how they do over the subsequent days.

How long should an attack be present

before randomization? On a practical basis, it is unlikely that we will be able to enter subjects into a trial that have their attack present for only a few hours. On the other hand, would we want to enter someone that has had their attack present for four, five, or six days?

On a practical basis, it would seem likely that the most likely subjects would have their attack present for one to three days.

Should we allow previous therapy? If an individual self-medicates 24 to 48 hours before randomization, is this acceptable? It may be acceptable if they have self-medicated with a short-acting analgesic that is completely washed out by the time of randomization.

However, if we don't allow any previous therapy because of the potential influence on the outcome of the trial, then, I would ask you to reconsider your concern for placebo-controlled trials.

If an individual has had an attack for 24 to 48 hours, and has not self-medicated, is there a

concern with entering them into a placebo-controlled trial?

If a patient is on previous therapy, should we withdraw them from that therapy, and can that be associated with a worsening flare of their disorder, and how would we handle that in a trial.

Lastly, the question, is there a difference in a disease course in individuals that have acute attacks on a background of chronic tophaceous gout versus those individuals that just have acute attacks?

So, the areas for discussion include the following, which I have discussed already some. Inclusion and exclusion criteria, superiority versus non-inferiority trials, especially the issue of placebo-controlled trials, what are the domains to study, what outcome measures and timing of the studies, and then other issues, such as stratification, concomitant medications, et cetera.

So, in conclusion, gout is a common disorder. You heard a lot about that yesterday. New therapies that provide improved risk-benefit

ratios should be studied and added to the armamentarium, and rigorous trial design is needed.

You will be hearing next from Dr. Cush, who will be discussing management of acute gout, and following that, a presentation by a company and their approach to a trial design in acute gout, and I think, all together, should provide an interesting background for today's discussion.

Thank you very much.

DR. GIBOFSKY: Thank you, Dr. Schiffenbauer.

Are there questions from the panel for Dr. Schiffenbauer? Just one from me, if I may.

In one of your slides, you asked us to consider whether gout is a medical disorder or a model of acute pain. Like light being a wave and a particle, can gout not be both?

DR. SCHIFFENBAUER: It could. I was asking the question because I think the implication is what should we consider as the primary outcome. If it is considered a model of acute pain, then, we have certain parameters that we use in acute

analgesia studies.

If it is considered its own entity, then, I think pain, but we may wish then to consider additional outcome measures, such as inflammation, and I think that is kind of what I was trying to set up and get from the Committee.

DR. GIBOFSKY: Dr. Hochberg.

DR. HOCHBERG: Thank you for an excellent overview of the issues. I guess one question, and I don't know if you will be able to respond to this, on your next to the last slide, you said that new therapies that provide improved risk-benefit ratios should be studied and added to the armamentarium.

I don't know what Dr. Cush is going to say, but in the vast majority of people who have gout, and I exclude from this the individuals who have contraindications to the use of nonsteroidal anti-inflammatory drugs either absolute or relative, the drugs have a pretty good benefit-to-risk ratio in this population.

So, does that imply that the Agency would

like to see agents which have a better benefit-to-risk ratio in the population which has relative and absolute contraindications to the drugs that are already in use, or would like to see agents which are quantumly beyond NSAIDS in terms of either efficacy or safety for the vast majority of people who have acute gout?

DR. HARVEY: Did you want me to jump in on this? Actually, we will see what the Agency sees, and, of course, we want to make sure there is safety and efficacy for the indication.

DR. SCHIFFENBAUER: We would always like to see quantum leaps in therapies, but I actually agree with Dr. Harvey's comment.

DR. GIBOFSKY: Any other questions from the panel?

[No response.]

DR. GIBOFSKY: Thank you. We shall see what we shall see, and now we shall see Dr. Cush, who is a member of the panel and also Chief of Rheumatology and Immunology at Presbyterian Hospital of Dallas.

Dr. Cush.

Management of Acute Gout

DR. CUSH: Good morning, everyone.

I have been asked to talk about the acute management of classic gout or the acute gouty attack, and it is my intention sort of to give a little bit of overview, but to focus on what has been done in trials and what are the outcomes and how that impacts on clinical trial design in the future.

A topic that was brought up yesterday by Jim and others is, you know, where are these patients and how do we get them in trials.

It is interesting to note firstoff, that most rheumatologists love gout. I mean it is a very interesting disease, it is easy to diagnose, the impact of our intervention is great. We feel good about ourselves when patients are very happy with their outcomes.

In fact, most of the giants in rheumatology, starting with Hippocrates and going up to the time of McCarty and Hollander and

Schumacher, and whatnot, have cut their teeth on gout as a career, and I think it is because it's an interesting disease, it has a direct cause, it has a biochemical and immunologic basis, and we have effective interventions, so this is why we love this condition.

Interestingly, however, very few of us are seeing a lot of patients with gout. We have patients who have chronic tophaceous gout in our clinic, we have an occasional patient who has chronic intermittent gout, but the vast majority of patients who have gout are being managed elsewhere, so although I wish they were in my clinic, they are not, and that is sort of a shame because we believe that, as a discipline, we have a great impact on these patients.

That was studied by Richard Panish in his paper that showed when rheumatology intervention was compared to a generalist approach to this condition, there was a shorter duration of symptoms, less hospitalization, lower cost overall, suggesting the value of a rheumatologic

consultation in such instances.

Hence, most of these patients are in the care of the primary care and emergency physicians. They are first line. That is, you know, people that darken the boxes, they go to their family doctor whenever they have a problem, and they don't know enough to go to a rheumatologist obviously, and if they did know, they probably couldn't get in to see us anyway. That is another issue.

But there are significant hazards here in that I think Marc's point about the effectiveness of therapy is so accepted at this point, it is absolutely true, however most rheumatologists are very aware of the fact that there is a large variability as to how patients are treated.

What I believe is the gold standard is probably not the gold standard out in the general community, and that varies, not only in our country, but also in surveys done in France and in Mexico and New Zealand, where there is considerable variability between the general practitioner, whether it be internist or family practitioner, and

the rheumatologist, and the orthopedist as far as their approach to gout.

What is unfortunate is that there is a surprising amount of misuse of these medications and inappropriate use of medications by the general practicing physician, so I think that to foster guidelines and new drug development is also to foster better education and, hopefully, better outcomes for patients who have this condition.

So, as stated, it is a disorder of monosodium urate crystal deposition. It has been around for years, started with Hippocrates in 450 B.C., when he described this as the king of diseases and the disease of kings. The burden to society is significantly great.

Roubenoff estimated 37 million lost days of work in the United States in 1981. Kim and cohorts, in their estimate of the burden of disease on society, said that gout costs us 27 million-plus dollars per annum for the management and care of acute gout, and this tends us to underestimate the true costs because this is mostly just men, it

doesn't include women, which are a significant minority here that are affected by gout, and it does not include a lot of the indirect and intangible costs of having such an impactable disease.

The epidemiology was reviewed yesterday quite well by Dr. Terkeltaub, but this NHANES survey, which was a telephone survey of the general population, was a bit of a surprise.

Most of the epidemiologic studies on gout suggested about 2.1 and 2.5 percent prevalence in the general population. However, when this survey was done--excuse me, 1 percent, going as high as 2.1 to 2.5 million people--when this survey was done and people were asked on the phone, "Have you had or do you have kidney stones," they found a much higher than previously reported prevalence, and they asked the same question of gout, and they found 5 million people who claimed to have gout.

Now, it is hard to confuse a kidney stone. It is a pretty certain diagnosis when a patient reports that. Patient reports of gout, however, are

notoriously inaccurate because the diagnosis, as made by their general practitioner, are unfortunately sometimes inaccurate, as well.

So, this is probably an overestimation of the true numbers, but it is probably somewhere between 2 and 5 million as far as the prevalence in society, and that prevalence does go up, as was pointed out yesterday, according to age, that men are mostly affected here, but that women in the postmenopausal era are almost equally affected.

This is a dramatic disease, and it is dramatic because of the abundance of inflammatory mediators that are produced at the time of the attack.

A wide number of mediators that cause this intense pain and inflammation, redness, and warmth, and whatnot, a number of cytokines, you can add this TNF and interleukin-8, and again, the list goes on and on and on as far as the amount of mediators that are present here.

Finding an effective therapy that will downregulate that and produce clinical symptoms is

really a gargantuan task, and it is actually surprising that we do as well as we do given the amount of inflammation that seems to emanate from these joints.

So, today, we are talking about acute gout, but, of course, gout is divided into several different forms, acute intercritical gout that appeared in between attacks when patients are quiescent and have no symptoms, and they are often not on therapy.

There is chronic tophaceous gout which was discussed in some detail yesterday, and then there is asymptomatic hyperuricemia, who has not yet had an attack of gout or uric acid nephrolithiasis. Then, lastly, there is renal effects of gout, as well.

Other publications talk about another distinction of acute or classic gout versus atypical gout, and atypical gout is also prone to having acute attacks, although they are not as acute, they are more insidious. They are more in women, they are more in older people who are on

diuretics and have hypertension and renal failure, and whatnot.

So, it is a sort of quasi-group. They tend to fall a little bit under this acute umbrella, but their inclusion in clinical trials could cloud things. So, again, the acute or classic attack of gout really usually is often referred to as acute podagra.

This is often a sudden severe onset of pain, warmth, inflammation. There is severe limitation of motion, patients are unable to walk, they are unable to have a sheet on it. It is really quite dramatic.

So, while Dr. Schiffenbauer points out that pain scales in the acute predictive gout are not much different than other pain models, it seems that gout patients scream a little louder, and it could be because men are wienies, I don't know. It could be that really it is more severe in its pain.

I tend to like some of the pain scales that are used in some of the clinical trials, because they tend to represent this almost like a

spinal tap 11, and they have zero to 4, zero being none, 1 being mild, 2 being moderate, 3 being severe, and 4 being extreme. That is sort of I think indicative of the severity of the attack.

Podagra historically was said to occur at the first joint in 90 percent of cases. More recent estimates are probably a little bit less, but podagra is the involvement of an acute inflammatory event that affects the first big toe or the MTP joint.

Some joints commonly involved early on are the tarsus, the ankle, and the knee, distinguishing it from other crystalline arthropathies and other acute onset of inflammatory events.

It is not uncommon for these people to have low grade fevers, high white counts, high sed rates and CRPs at presentation. Patients will often have monoarthritis as the first attack, but then with repeated attacks, will ascend from their lower extremity upwards and may have oligoarticular and polyarticular presentations later on in the disease especially when tophi form.

The initial presentation of polyarthritis is more often seen in the elderly, in women, and those who have mild proliferative disorders, also, in patients who have a transplant and are receiving cyclosporine.

There are many precipitants to this - inactivity, surgery, alcohol, infection, drugs, and whatnot. Untreated attacks can last up to 14 days, although there is quite a significant amount of variability there according to who you read, but that is what my experience is.

Those who have an attack are at high risk for subsequent attacks. The majority will have another attack within a year, and it is estimated that 78 percent will have another attack within two years.

An interesting study done by Bellamy and coworkers in Canada, and published in 1987, looked at the natural history of gout in 11 individuals who had an acute attack of podagra. There were 11 volunteers who had this acute attack. Two withdrew before the full course of therapy or of observation

I should say, because of severe attacks, and went on to receive indomethacin.

It should be noted that these 11 patients who had acute gout, there were 2 who had tophi at entry, 5 who had a history of nephrolithiasis, 2 who had a history of both. All had prior attacks with a median of 4 prior attacks in the 7 years prior, and that occurred usually with a median of within 4 years.

Nine were on allopurinol and 1 was on a uricosuric agent. It is unclear as to whether those drugs were continued during this trial. But, nonetheless, when they observed these people, they showed that pain was improved by Day 5 in the majority of patients, that swelling was improved by Day 7, that tenderness was improved in 7 out of 9 patients by Day 7, but 2 patients continued to have persistent pain. But only 3 people had noted complete resolution of their symptoms by the end of the 7-day study.

So, again, pain and swelling and erythema and warmth all began to improve after Day 3. A

significant improvement was really seen between Days 5 and 7, although again complete resolution was not had in all.

At entry, these patients had a mean pain score of a little less than 4, a little less than extreme, and at the end of the study, 7 days, the mean value was only about 2 or moderate level. So, again while these patients got better, this is not complete resolution of the disease.

The implications here are significant for trials, first, what is your endpoint for these attacks and when will get pain get better on its own, and what are the outcomes that we should do in looking at that.

So, laboratorywise, again, we should note that, you know, hyperuricemia is a hallmark of the disease, however, studies have shown repeatedly that up to 50 percent of patients will have normal uric acid levels at the time of acute gouty presentation.

Leukocytosis is common, elevated sed rates and CRPs are seen, often because of an intermittent

inflammatory process, chronic inflammatory indices, such as a low albumin, anemia are not seen.

Cytokine levels have been measured and shown to be elevated in patients, and there are classic x-ray findings that can be seen early on with soft tissue swelling, later on with development of punched-out sclerotic, overhanging edge type erosions.

These are the patients who have tophi in different forms, the helix of the ear, over the elbow, and severe chronic tophaceous gout over the hands. The difference between these and nodules is that they seem to come to a head and have a propensity to break through the skin and exude this chalky substance that is very, very rich in monosodium urate crystals.

Their incidence has decreased over decades, presumably with better therapy, however, they are seen in a significant minority of individuals. It is estimated it takes up to 10 years for a patient to have gout, to develop clinically manifest tophi.

They are most commonly seen over the elbows, but can be seen in the hands, feet, and ears. They will damage tissue and bone and whatnot, and therefore, their presence is alarming, not only because of their damaging potential, but also because what they indicate as far as total body urate load.

Uric acid, we talked about yesterday. Again, up to 50 percent of patients will have normal uric acid levels at the time of attack. The mechanism of this are probably not understood. They are probably mediated by inflammation, suggesting that maybe inflammation, including IL-6 may enhance renal clearance of uric acid, and it's possibly why we see that.

Another interesting factor is the negative association between gout and rheumatoid arthritis, a good teaching point for our residents and people we teach, because often patients will come with both diagnoses, and you can't have both, and there are actually good reasons for that, or at least there are some suggestions for that, some which

involve the role of rheumatoid factor possibly in blocking interactions between IgG and Fc receptors, possibly the role of just inflammation in cytokines in enhancing uric acid excretion, that also is somewhat protective, hence, the exclusion of patients with a diagnosis of RA would make sense in an acute gouty trial.

How does one diagnose gout? There are two ways. One would be the American Rheumatism Association criteria of 1977, as was reported by Wallace, where you either have to have crystal evidence of monosodium urate crystals in either the joint or in a tophus, or any one of the 6 clinical following features.

That would include more than one acute attack, maximum inflammation within one day, erythema over joint, acute podagra, history of podagra, unilateral tarsal involvement, tophi, hyperuricemia, asymmetric swelling on x-ray, subcortical cysts without erosions, and culture-negative inflammatory arthritis as a means of a clinical diagnosis without evidence of crystal

identification.

In a more practical manner, this is what I do in practice, I think most of us do, is patients present with acute or recurrent mono or oligoarthritis, and then you confirm the diagnosis by crystal identification.

In the absence of crystal identification, one can substitute with probably not to the same degree of certainty, but I think enhanced certainty, any one of the following. That would include a history of recurrent disease, a history or evidence of hyperuricemia, and lastly, x-ray evidence of gouty damage with sort of typical x-ray of gout seen on x-ray.

So, here again, the acute podagra episode mediated by a urate crystal, in this case taken up by a poly, and again, this is fairly miserable arthritis. I mean the onset of many of the other arthritides we take care of is often not as dramatic as that seen, and we don't see rheumatoids with faces like this. We tend to see only our gout patients who look like this when they come in.

So, the management of gout, which was discussed yesterday, mainly, the chronic management, the acute management of gout is nonsteroidals, steroids and colchicine.

There are some problems with this, and this goes to I think what Marc Hochberg brought up earlier is that our therapies work really well and that the benefit-to-risk ratio seems to be quite acceptable.

In fact, that is true, but there are risks associated with this, and those risks are maybe more compounded in patients who have risk factors, who have baseline or background diseases that enhance the toxicity of the agents that we commonly rely upon to use in the management of gout.

So, I think this is sort of the reason why one needs the development of newer and possibly safer therapies with at least equal efficacy, if not better efficacy, but again, if our past efforts have been very good, then, why not shoot for that.

The management certainly should begin with the confirmation of diagnosis. This is what we do

in rheumatology practices. This is what is not often done in the emergency rooms and in the general practitioner's office who may not have again a detailed understanding of the condition.

Also, the management of acute gout also is the beginning of the prevention of subsequent attacks, and that is modification of behaviors and drugs and whatnot that may contribute to such activity.

There are FDA-approved therapies for the management of gout, and there are a lot of therapies that are unapproved, that have been tried in trials, and obviously, during acute gout, you would want to avoid drugs that lower uric acid levels, such as uricosuric drugs and even allopurinol.

There are regional differences as to how this is managed. Nonsteroidals, if you read publications and talk to physicians, are the preferred drug of choice in the United States and Canada, New Zealand, and Australia, however, in print, there is a widespread preference for

colchicine in France, and many of the European Union nations who also feel that the use of colchicine is not only effective, but is also diagnostic.

In many instances, for instance, in this one survey in France, 61 percent of the physicians preferred colchicine alone, but 32 percent of that same cohort preferred the combined use of colchicine with a nonsteroidal.

The duration of therapy is going to vary according to the patient's symptoms, but could be as long as a month. It is quite interesting, though, as historic as this disease is, and as prevalent as it is, that there are no formal guidelines that have been tested and/or advocated, although I was reading Dr. Terkeltaub's New England Journal article last night and came across a Dutch web site for general practitioners that has guidelines out there, and several medical schools have their guidelines for local use, but again, none of these have actually been tested or been even rigorously developed using evidence-based

methodology.

So, the drugs that we do use in the management of acute gout have significant effects, there are well-known dosing regimens that can be used, but there are also well-known toxicities that need to be kept in mind in the choice of one's therapy.

This is a publication that I was involved with in the management of acute gout. The first question is nonsteroidals, can they be used or are they contraindicated, does the patient have renal insufficiency or history of peptic ulcer disease, congestive heart failure, or intolerance to these drugs, and, if not, then nonsteroidals are the preferred agent of choice.

However, if those are contraindicated, then, the next question is can you use the corticosteroids, and, if not, then what you probably should do is use the corticosteroids. The question is how much and where and when and whatnot. On this, you base your decision on how many joints are involved.

If it's a monoarticular presentation, one would consider the use of intra-articular steroids, less toxic, more effective, rapid onset of effect. However, if it's polyarticular presentation, one could go to either oral or--excuse me--that is supposed to be intramuscular administration.

If, however, corticosteroids were contraindicated, brittle diabetes or brittle congestive heart failure, one could advocate the use of oral colchicine, and only oral colchicine.

So, colchicine is certainly the most historic drug used in the management of gout. It is talked about as the first drug for gout. It's an alkaloid of the Colchicum species. It has significant anti-inflammatory effects, thought to be mediated by its ability to inhibit microtubule formation and basically poly activity.

The half-life of this drug varies widely according to who you read. It is as brief as a few minutes. Its plasma half-life is certainly less than an hour, it is as short as 19 minutes, but it can be as long as 16 hours, because it does seem to

bind to tissues, especially polys and microtubules, and stay around for as long as 10 days.

So, again, there is a wide variability here. It is found, because it is lipid soluble, it is found in other tissues in high concentrations including the liver, spleen, and intestine. It is excreted in the urine, in the bile, and undergoes some degree of intrahepatic recirculation.

It is metabolized by demethylation using cytochrome 3A4, which is also responsible for the metabolism of other drugs which have been linked to the toxicity of colchicine use especially erythromycin, ketoconazole, cyclosporine, and most recently, the statins.

These drugs do cross the placenta and are found in breast milk. They are not dialyzable. They have many off-label indications besides gout, pseudogout, amyloidosis, FMF, many skin conditions including Behcets and Sweets syndrome, and it goes on and on.

The biologic effects of colchicine are numerous, but again its mainly its effect on polys

and poly activities with adherence and degranulation, but it does inhibit the expression of adhesion molecules, the generation of cytokines and chemokines that are probably involved in again this inflammatory process.

There are many advantages to using colchicine, it has a lost history. It works in both acute gout, it works as prophylaxis in chronic gout, and prophylaxis when starting hyperuricemic therapy.

It is said to have a diagnostic specificity of 96 percent and sensitivity of 70 percent. It has a very fast onset of action when used IV, although it is longer when used in the PO form, and this is said to be certainly faster than what is seen with corticosteroids either as intra-articular or intramuscular, which is certainly better than PO corticosteroids.

Lastly, I think nonsteroidals tend to have their effects a little longer. There is certainly an advantage in the management of the patients who are NPO and not able to take anything by mouth,

surgical patients and hospitalized patients, and those who are intolerant or unable to take nonsteroidals because of contraindications.

These drugs are cheap. Yu, in a retrospective analysis of 540 patients, basically showed that the results of colchicine therapy were excellent in 82 percent of individuals and satisfactory in 12 percent, and only poor in 5 percent, and there were few episodes of intolerance, no cases of renal or hematologic toxicity, and this was over an extended period of time, over 20 years, in 540 patients.

It has been studied going back to 1939, when Lockie tested colchicine in patients with gout, 75 patients, and compared the effects of colchicine in those patients to other rheumatic disease including rheumatoid arthritis and psoriatic arthritis, and whatnot.

Interestingly, all of the gout patients responded to colchicine, whereas, none of the other arthritides did. They do not talk about their outcomes that were used in that trial, but it

nevertheless shows again the specificity and selectivity of a colchicine response.

In 1967, Wallace tested 120 patients, 58 of whom had acute gout, which was originally defined as an elevated uric acid level with a current arthritis. Fifteen of these patients had tophi, and they were treated with colchicine orally or by IV, roughly split, in the total 120-patient group.

Major resolution of joint inflammation within 48 hours was the prime outcome with no worsening in the next 7 days. In the gout population, 76 percent of patients resolved, whereas, in the other population, only 3.2 percent of patients resolved, again suggesting the specificity of response here.

Acute gout management, I don't think I need to go through this a great deal, most of us know this, but it is 1.2 or 1 mg initially, and then a dose every 1 to 2 hours until GI symptoms develop or until the patients are better.

Ahearn, in his publication, it was a

placebo-controlled trial comparing colchicine in gout, showed that 64 percent of patients responded within 48 hours. That compared to 23 percent in the placebo arm.

They both had again progressive improvement over the next 36 hours, however, colchicine and related GI toxicity and diarrhea developed within 24 hours in most patients, so often the GI symptomatology and diarrhea, which was really quite severe, has its onset before the onset of clinical improvement.

I heard yesterday Marc's statement that patients are still very happy with colchicine outcomes because they would rather deal with GI toxicity than the pain of gout, which is a testimony to how severe the pain of gout really is.

Again acute use is reserved for patients who cannot tolerate nonsteroidals and steroids. Dr. Wortman has a recent publication where he states, quite interestingly, that he prefers nonsteroidals in the management of acute gout, however, he does prefer the use of colchicine when

patients don't yet have an established diagnosis, such that he can use colchicine almost as a diagnostic test.

So, when would one use IV colchicine? Well, in my estimation never, but it should be used or advocated when a rapid response is needed, when oral use is precluded and when nonsteroidals and steroids are contraindicated.

The problem is that there are no warning signs here as there is with oral colchicine. The toxicity sort of depends upon how much you give over time and what your doses are. The recommended doses are either 2 mg initially, followed by 1 mg every 6 hours, for a maximum of 4 to 5 mg.

Another regimen would be 2 mg IV as one single dose, or a third regimen would be 3 mg as one single IV dose.

The problem is that there is significant amount of toxicity associated with this. It can be as simple as extravasation into the local tissues, which causes significant irritation if not tissue necrosis, but it can be severe as death.

A report coming out of the Office of Drug Safety here at FDA, they detailed 20 deaths that occurred in a recent time period.

This is a listing of 23 publications, just by literature search, that give evidence for severe toxicity, episodes of suicide, and mortal outcomes in patients who received IV colchicine, suggesting that the utility and the use of this approach should be severely questioned.

In this Bonnel article, well, actually before that, I asked Joel to tell me, if he looked at the Med Watch system, what did he come up with, and just looking at just the Adverse Event Reporting System, since 1990, in the system, there are 90 deaths associated with IV colchicine.

Now, those are not confirmed, we don't know if there is duplicates in there, we haven't researched those, so that is just a ballpark figure suggesting that this is a serious problem.

Interestingly, during the same period, there were 429 deaths associated with allopurinol, but again there are a lot more issues going on

there. Allopurinol has far greater uses, wider uses than does colchicine.

In its report by the Office of Drug Safety in Bonnel, there are 20 deaths over a 17-year period. Most of these were taken from the Adverse Event Reporting System, but some from the literature.

There were mostly males, 11 males and 8 females, 17 patients, and they ranged from 50 to 90 years of age. There were two cases of FMF, and the rest were gout. All exceeded the recommended doses of 2 to 4 mg. The range went from 5.5 to over 19 mg as a total course.

Adverse reactions that were seen included thrombocytopenia, leukopenia, pancytopenia, agranulocytosis, aplastic anemia, tubule renal failure, and DIC. Death occurred within 1 to 40 days, and 80 percent of these patients showed evidence of bone marrow depression.

There were risk factors in 13 of these patients including the elderly, pre-existing medical conditions, the use of background

nonsteroidals, and recent oral colchicine use that was then compounded by follow-up therapy with IV colchicine use.

It was clear from their review of the warnings, precautions, and contraindications listed in the package insert or in prescribing guidelines in any major publication were not followed or were misinterpreted by the prescriber.

Acute toxicity with colchicine can be again limited to just the skin. Many suggest that this drug should not be given IV unless there is an indwelling catheter that had been firmly established.

Symptoms could begin as tightness in the chest, difficulty swallowing, abdominal pain, nausea, vomiting, diarrhea, arthralgias, myopathy, and then lead to severe shock, oliguria, paralysis and delirium.

The mechanisms by which these patients develop these multi-organ involvement and subsequent death has really not been fully elucidated. Again, the labs are dramatic, often

with severe cytopenias and the development of renal failure and DIC.

Fatalities have been seen with as little as 1 mg IV in patients who have been on background therapy and then received this and had obviously other risk factors.

Rhabdomyolysis has been reported especially in end-stage renal disease, and the patients who were felt to be at risk are those again who are older, who have renal failure, those who have been previously taking PO colchicine and now get switched over to the same dose of IV colchicine, those who are on background cyclosporine or tacrolimus, those on grapefruit juice, and those on statins.

Again, you can see the different stages of intoxication could begin with GI symptoms and dehydration, and then progress to more severe manifestations in the first two to three days. If the patient is lucky enough to recover, leukocytosis and allopecia will ensue.

So, guidelines for use I think should be

reviewed and always advocated. It should be severely restricted as far as its use, whether restricted to a particular discipline or an individual, or to be banned outright either by institutions or maybe even by this body.

In Great Britain, it has been removed from the formulary totally. In many hospital systems around the country, it has been removed from the formulary totally. I was in a hospital last week where a very well-known rheumatologist opened some mail while I was sitting in his office, and he got very upset. He said, "Darn, look at this, my favorite drug has been taken off the formulary because we had a recent death, because some knucklehead inappropriately used IV colchicine."

A drug that he loved to use, that he was very skillful at using, this is a very good rheumatologist, I am sure he knows all these guidelines, other people have now taken this drug away from him, and he can no longer use it in his hospital.

Again, single IV doses should not exceed 3

mg as a single dose, and 2 is probably a better dose. Cumulative doses should not exceed 4 to 5 mg over a total of 7 days. When one looks at the patients who died and had serious toxicity, often it was more than 1 mg per day over a 7-day period, that patient got into trouble, and, in fact, going higher than 0.5 mg per day for a 7-day period put patients at risk.

It should be given by IV catheter. If IV use is to follow chronic PO therapy, and used to sustain the patient, it should be done at basically half the dose. If you are going to follow up IV therapy with PO therapy, you should wait 7 to 10 days before initiating PO therapy.

Reduced dosages should be used in the elderly, in those with liver disease and renal disease, those with prior PO colchicine, and it is certainly contraindicated in those who are pregnant, who have combined renal-hepatic disease, who have very low creatinine clearances, and who have evidence of biliary obstruction.

Treatment is often difficult obviously

with drug cessation, promoting intelligent use, it is not dialyzable, cytopenias can be managed with growth factors in some instance, rhabdomyolysis should be managed, as it usually is, with fluids and alkalization, if necessary, and there have been some experimental therapies with Fab-2 fragments to inhibit and to bind, but this is an experimental tool that is being used.

Moving on to corticosteroids and intra-articular and intramuscular use, they certainly have benefits equal to nonsteroidals. They are felt to be overall less toxic when used acutely and intermittently, and again have significant benefits.

There are, however, some issues, that there is no standardization as far as dosing, which form is best, what is the best route. It is often good in patients who have contraindications to receive nonsteroidals, and that includes heart failure, renal failure, GI bleed, or patients who have monoarticular presentations in whom a intra-articular injection would make more sense.

Toxicity can be significant, hyperglycemia, hypokalemia, fluid retention, and it is frequently reported that patients who receive corticosteroids get better, but then a few days later or maybe a week or two later, they actually rebound where they get another flare of gout.

Prednisone orally has been used with doses of 30 to 50 mg being advocated for up to a week and then tapered over the next week or so. Again, there is this issue of rebound.

ACTH is probably the best studied of these, either 40 or 80 mg--excuse me--international use as in a single injection. Other dosage forms include triamcinolone, acetonide, and betamethasone, 7 mg.

I have listed a few studies here that look at the value of ACTH therapy as compared to Indocin or Diclofenac here, and you can see that basically, ACTH seems to perform very well. It had a faster onset than Indocin, and Indocin certainly had more toxicity, was compared head to head over here.

When it was an uncontrolled trial, 97

percent of people were better by 5 1/2 days. When compared to triamcinolone, both groups, the ACTH group and the triamcinolone group, responded by Day 8, but the triamcinolone group had fewer rebound episodes and required less re-treatment.

Then, Werlen showed that when comparing these two different steroid forms, the Diclofenac and steroids outperformed the nonsteroidals in their trial.

So, nonsteroidals have been advocated, FDA approved, including indomethacin, naproxen, and sulindac. Many have been tested in clinical trials, most of which have been open label. The benefits of nonsteroidals are that they certainly have a fast relief of onset compared with colchicine, PO colchicine, not IV.

It is estimated that 2 to 4 hours it takes for people to get better. With indomethacin, that would not be complete improvement. It is less toxic when prescribed appropriately and better tolerated than certainly colchicine. They are widespread in their use and most docs are more

familiar with the proper dosing and use of nonsteroidals than they are with colchicine and IV colchicine, and certainly in many instances, there are very cost effective.

I believe the representative from Merck will review the combined results of the etoricoxib study that was reported recently at the American Pain Society, but all of this to say that etoricoxib and COX-2 inhibitors have been tested in gout in two studies, and submitted an analysis of both or a combination of both, and they have showed using two primary outcomes here that etoricoxib compared very well to Indocin, so while they both had significant benefit, the real benefit was seen with less toxicity in the etoricoxib group compare to Indocin as far as hypertension, diarrhea, and CNS or headache.

Analgesics have also been advocated in the treatment of acute gout, and that includes the use of topical ice where it has been shown that patients who received ice had better outcomes as far as swelling and pain, and ketorolac.

Actually, this fellow Shresta was one of my residents at Parkland, he did both of these trials at Parkland, and he used ketorolac, and his time points were very short time points, 30 minutes, 60 minutes, 90 minutes, and 2 hours.

He showed in this open label trial and a double-blinded, randomized, controlled trial against Indocin that it performed very well, either equal to Indocin or certainly significant by 90 minutes or 2 hours in both trials.

There was, however, in the second trial, some rebound in patient who received the ketorolac after 6 hours.

I have a listing for you in the next two tables, the trials that have been done, open label trials and controlled trials, in the management of acute gout. This is basically for your education to show you, number one, the design and the number of patients, but to look at the primary outcomes that were used in these trials and the time points for evaluation.

You can see that most of these used pain

or joint exam findings, tender joints and swollen joints, as outcomes, but pain usually in VAS or Likert scales, and the days and times of evaluation ranged from 24-hour evaluation to--or Shresta, he did these at 30 minutes, 60 minutes, and 90 minutes, but one day all the way up to 7 days here.

In the next trial, these are controlled trials, comparing mostly nonsteroidals, some of these are steroid trials and ice trials, and whatnot, and you can see again most of these required pain outcomes and, the top one here, a 50 percent reduction in pain, mostly going to the reduction in pain level, or reported just changes in pain level, usually is reported by either VAS or Likert scales.

Again, the time points that were usually looked at were 1 to 8 days in most of these trials.

So, the considerations as we go forward is how does one establish a diagnosis, would it be solely based on prior evidence or current evidence of crystals as a means for diagnosis.

Would you rely on ARA criteria, either

crystals or the clinical criteria, or would you use the much more practical approaches as I do in clinic, what is the duration, does someone come in with two weeks of symptoms and new gout, or must they have established gout over time, what does the duration of attack have to be before they get in.

In some instances, patients had to wait 5 to 7 days to get in. This is sort of a problem, because again that is the maximal amount of pain. You want to get these patients in as soon as possible.

Con meds are issues, as Joel talked about. I think most patients will come to you on some degree of pain medicine whether they be nonsteroidals or other pain medicines. Steroids obviously I think would compound things unless it was a steroid trial, and allopurinol should be stopped at entry.

Time assessments. The window here is much shorter. This is not like the trials we were talking about yesterday. We were looking at 3 months, 6 months, and 12 month outcomes. Here, I

think we are looking at 1-day, 2-day, 7-day outcomes, and the extended outcome may be anywhere from 14 to 30 days.

The primary outcome is always going to be pain, I mean there is no doubt about this. I don't know that there can be much argument here. This is an incredibly painful condition, and that is what patients want. That is what we accept clinically when we see these patients.

There are other secondary measures that one can look at and I list those for you there, and I would advocate these are rescue medicines in any regimen whether it be placebo-controlled or an active-controlled regimen.

This is my suggestions for a clinical trial. Number 1, I see as guidelines for actual numbers, I think would be Smart in this instance. Obviously, they would be short-term trials, so I think that the first applies here. We are not going to have many people treated with acute therapy for over a year.

I believe an active controlled trial,

looking for a non-inferiority design largely because of what Marc brought up earlier, which is that the therapies we have are very effective. You know, to go against a currently approved therapy wouldn't make a great deal of sense, and use a non-inferiority design, that you have obviously double-blind and active controlled.

Patients should have a diagnosis of gout, and I think that although I like my method of diagnosis, I still think you have to go with something that has been tested and held to be true. ARA criteria have a sensitivity of 87 percent or 84 percent, and specificity of 100 percent if you include crystals.

The acute gouty attack should be seen within a certain period of time, certainly within three days. The trial length could be up to two weeks, and visit frequency I think would have to depend on the expectations of the drug and its onset of effect.

One thing that I was thinking about, that is not on the slide, but is a common issue in

clinical trials, is that patients have a run-in period. They are seen, they are screened, they are consented. You get labs, they come back a week or two, or three days or two days later, that is a problem here. These people hurt today.

I think that inclusion criteria have to be liberalized to allow for people who may be entered into a trial who have renal failure and you don't know about it, who have LFTs that you don't know about, who have, you know, because they didn't reveal the fact that they are an alcoholic, the ideas that they need to get in, I think you should protect the trial as best you can with Smart criteria, but I don't think you should impair enrollment in these trials by clinical inclusion criteria.

Obviously, age greater than 18, the diagnosis of gout, an acute attack should be defined, and I think that should be one of the outcomes here, not only how long an acute attack lasts, but whether they have subsequent acute attacks.

Mono/oligoarthritis are preferable at entry. Polyarthritis I think should be excluded for several reasons. One, it could be something else. Two, the polyarthritis tends to fall more in that atypical gouty group, older women, more insidious, older, mostly women, more insidious attacks, nodal osteoarthritis, a lot of other factors going on there, and their response to therapy may not be the same, so I would tend to exclude polyarticular presentations of gout in such trials.

Activity needs to be assessed, and activity can be easily assessed by just using the cardinal signs of inflammation, so tumor, rubor, dolor, or calor, pain, swelling, redness, and warmth, and improvement in two out of four, or three out of four as very objective means of outcome.

Exclusions, I think absolute exclusions should include polyarthritis, an excessive alcohol use, renal insufficiency, if known, background aspirin, if known, cyclosporine, rheumatoid

arthritis, transplant, active infections, dietary restrictions, and uncontrolled hypertension might be certain obvious issues you would exclude.

What is on the table, and I think very uncertain, are background use of nonsteroidals or BC, diabetes, heart failure, tophi, nephrolithiasis, previous or current narcotic use, previous or current anticoagulants, background nonsteroidals, allopurinol, probenecid, sulfinpyrazone, hospitalized or immobilized patients, those that are unwilling, and, my favorite, those who are currently involved in litigation.

So, primary outcomes I think are clearly going to be patient derived and pain. I think that pain can be self-reported measures of pain. We heard presentations at our pain advisory meeting about the use of PDAs and direct patient entry of data.

It is real-time, more reliable, gives you I think a true assessment of what is going on. It can also give you a more reliable assessment of

time to onset that may not be easily achieved in a recurrent physician visit kind of assessment.

Secondary outcomes can be both patient and physician derived. That will include global assessment of the disease, global response to the drug, complete resolution of symptoms, time to resolution of symptoms, what happens in an index joint, if one can be identified as far as the four cardinal signs of inflammation, swollen joint score, tender joint scores on zero to 3 scale, the need for rescue analgesics, inflammatory indices of sed rate and CRP, uric acid could be also looked at although I think less important, functional measures, and then comparison with the active drug as far as the safety and toxicity profile.

So, that was a mouthful. I will end there.

Thank you very much.

DR. GIBOFSKY: Thank you very much, Dr. Cush.

Are there questions for Dr. Cush from the members of the panel?

Dr. Weisman.

DR. WEISMAN: Dr. Cush, what is your formula for managing patients with acute gout that is complicated? Transplantation comes in with a creatinine of 2, already on steroids, and so forth.

DR. CUSH: Well, the more complicated they are, the more I tend to rely on steroids in management, so if they have transplants, and if they have renal insufficiency, and they are hospitalized and they are NPO, I think steroids is the major issue.

It has often been advocated that in patients who have contraindications to using nonsteroidals, that you can still use them because you are unlikely to get into the significant trouble one sees with nonsteroidals, whether that be GI or hematologic or renal, because you are using short courses of therapy.

However, I think that is probably overestimated and that most patients don't need three days of therapy. They probably need more like seven to 14 days of therapy, and there the risks

are real.

So, I think complicated gout may require parenteral administration of medicines, more use of steroids. I tend again not to want to use IV colchicine.

I think getting smarter about prevention of subsequent attacks and using combinations of whatever the patient can tolerate to treat the acute attack is the smartest way to go, but then again, you know, complicated courses are often because you can't get them under control.

The real struggle I don't think is as much in the management of the acute episode as once you get them under control, how do you keep them control, because what complicates them are the factors that bring out these more recurrent attacks.

DR. WEISMAN: Would you include them in clinical trials?

DR. CUSH: Well, again, I alluded to some of that by saying no for transplant, no for cyclosporine, no for a lot of difficult situations.

I think these acute trials could occur in patients who have well-controlled intercritical gout on no therapy, or well-controlled intercritical gout on some therapy.

It could occur in well-controlled tophaceous gout and then has an acute attack, but patients who are chronically out of control with inflammation and swollen joints and whatnot, that can be a more problematic group, and they are more likely to be in that tophaceous gout group. Again, those might need to be excluded.

I think again to liberalize patients, so that they don't have to undergo, for instance, a lab screen, that requires them to return in 24 hours or a week, would be a horrible thing, because it would deny those people access to treatment which they desperately need today.

DR. GIBOFSKY: Dr. Hoffman.

DR. HOFFMAN: That was a great and very thoughtful review, Jack. Thank you.

I would like to hear your thoughts on a couple of points that you mentioned and guidelines

you suggested. If I understood you correctly, you would stop allopurinol in patients who came in with acute gout.

We have all seen patients who have recently had allopurinol started and have precipitated an acute attack, and I am not sure that that attack is in any way, other than for that association, different than other attacks or that it would respond differently to the agent being tested.

So, I am not sure why someone would change the dose that the patient came in on, the allopurinol dose rather than just continue what they were on and treat the acute attack in testing the agent of interest.

DR. CUSH: I think it is a matter of how one is taught, I don't think there is a lot of science here. I think there is a lot of hand-me-downs as to what works. I mean I have always been taught that it should be stopped mainly because you want to stop the mobilization of tissue stores as much as possible to give you the best

chance of acute resolution, that if they continue on allopurinol, you may prolong the attack.

Again, I don't think that is as well studied as I wish it were. That is certainly an issue, whether or not patients should be continued on whatever background therapy they are on, whether it be allopurinol or diuretics. Obviously, there are drugs that may contribute to either that event or maybe even the prolongation of that event.

My view is if they can safely be stopped, then, what is the hazard in it, are you hurting the patient down the line as far as their ultimate control, would they fall out of control by stopping that 300 mg or 100 mg a day of allopurinol.

DR. HOFFMAN: I don't know the answer to that either, but I think it is an issue that remains perhaps contentious.

DR. CUSH: Right.

DR. HOFFMAN: Along the same lines, since the significant minority of people, you have got a great handle on the literature and can probably inform us, but I am thinking that there are some

studies in the past that have suggested that when you look at all gout, that perhaps as many as 30 percent of people have polyarticular gout.

You might comment on whether that is accurate or not, but if it is a significant minority, why would one want to exclude polyarticular gout in a trial especially if one of your standards for inclusion was crystal demonstrated gout?

DR. CUSH: If crystals were your identifying factor, I think that you would be a little more certain, but you could identify crystals, and still not know whether that is acute polyarticular septic arthritis, as well. So, that is an issue.

I think what is clear from what I have read and looked at is that in the initial presentations, not someone who has established gout and has recurrent disease, but in the initial presentation, polyarticular gout is very, very uncommon except for in the population I mentioned - women, mild proliferative disorders, elderly, and

those receiving cyclosporine.

Otherwise, it is actually really small, it is probably in the single digits. By "poly," I mean four or more joints. You know, mono and oligo is really I think where 90-plus percent of the patients exist. I think that there is more diagnostic certainly in that restriction.

If one allows polyarticular gout, I think you would need to make sure that you are not dealing with other issues, whether it be another crystal, whether it be background issues that may complicate response to therapy.

So, I mainly exclude them because I think it is an uncommon aspect to the disease, and there are so many patients, you don't need those to do the trial well.

DR. HOFFMAN: So, you wouldn't exclude oligo.

DR. CUSH: No, I would not exclude oligo. I think that is a very important inclusion.

DR. HOFFMAN: Finally, if the chairman would allow me a final question, I would just like

perhaps your opinion and some of the other experts on the panel about what I think is a bias in the literature.

That is the nonassociation of gout and rheumatoid arthritis. I actually don't believe that at all from my own practice because I would submit that most rheumatologists who see a patient with a flare-up of RA, and are concerned about a comorbidity, might or might not aspirate the joint to rule out sepsis, but probably don't personally do synovial fluid analysis.

DR. CUSH: Right.

DR. HOFFMAN: But having done that myself, I have seen a number of cases of patients with RA and gout, of course, as well as pseudogout, and I am not sure how robust that literature is, and since the notion has been in the literature, then, there has been a story, perhaps fantasy, that has grown up around it regarding rheumatoid factor and inhibition.

DR. CUSH: Well, I would agree it is not a well studied matter. I think it is somewhat urban

legend, rheumatology legend that has passed on.

My own belief is that it is true, and that stems somewhat from observations and doing clinical trials where I don't know why uric acid was being done, but I have done several trials where RA patients, uric acid levels were being done, and it was clear that uric acid levels would go down when RA was at its worst.

That was curious to me, and that is why I think some of the more recent data about this negative association and maybe why that occurs associated with IL-6 and whatnot rings true.

I think it is an important teaching point because I think in the general practice community where people are seeing arthritis patients don't know well how to diagnose these, patients come to us all the time with, "Doctor, I have gout, lupus, and rheumatoid arthritis."

"I am sorry, ma'am, you don't. Firstoff, you are too young to have gout and you definitely don't have lupus."

For me to propose that the two can

coexist, I do propose that septic arthritis and gout often do coexist, I think would be misleading and miss a prime teaching opportunity to the general public, which is that you either have one or the other, and if you have both, let's report it.

In fact, if you looked at the reports in the literature of combined gout and rheumatoid arthritis, they are less in number than the numbers of combined gout and septic arthritis.

I still think your point is right. I think that most rheumatologists, when they see an acute rheumatoid who has one or two swollen joints, rather than aspirating that joint, treat it. And how do they treat it? More nonsteroidals, more steroids, and whatever.

So, the possibility I think still remains and I think for someone to study in that matter by vigilantly looking for it would be an important contribution to our literature.

DR. GIBOFSKY: Dr. Cronstein.

DR. CRONSTEIN: Jack, again, that was a

terrific review and very thoughtful.

One of the things that you mentioned was the need for very rapid assessment and enrollment of patients, so this might preclude I guess a more thorough evaluation of the medical status, but since many of the drugs, whether they are comparator agents, all the nonsteroidals, for example, can exacerbate hypertension and renal insufficiency, I am just wondering if you could elaborate on how you might go about doing this, because this is going to be a problem.

DR. CUSH: And figure this into the equation. If this trial is done by me, and by those of you around this table who do clinical trials, this won't be as much of an issue, because we will actually spend an hour with the patient, we will do a very careful history, we will do a very careful exam.

In that hour, we could actually have labs back and see what the creatinine and LSCs are, and whatnot. But the problem is I don't have these patients in my clinic, I am not going to treat that

many acute gouts this year. If you are going to do this in emergency rooms, in family practice clinics where they are seeing patients every 8 to 10 minutes, you know, these guys don't have the time to do this kind of detail, and so you are going to get a real world view of these people including some of their comorbidities and some of their background therapies.

You know, the FDA and the product manufacturers have to accept a higher degree of toxicity that may be associated with such an approach, but to not do that is to maybe deny people who really need therapy right now some intervention.

How long can someone who has acute gout, where they can't have a sheet on their big toe, or they can't walk, whether it's a mother who is taking care of kids or a businessman who has a trip tomorrow, and whatnot, I think it is cruel and unjust.

I think that I would point to the higher good, which is go for patient relief and now, and

accept again a more real life population except that I will enroll them now, get my labs, and maybe we have to stratify those people post hoc for patients who had uncontrolled hypertension, for patients who had renal insufficiency, people who were diabetic, and whatnot.

DR. GIBOFSKY: Dr. Terkeltaub.

DR. TERKELTAUB: Thank you for that review.

I wanted to point out one item about gouty inflammation, and that is, that it actually, pathogenically, is very well characterized. I mean not only do we have the etiologic agent as opposed to, you know, not knowing the primary etiology of RA, but the major inflammatory mediators including IL-1, TNF-alpha, IL-8, the signal transduction cascades including P38 and of Kappa B inhibitors, the effects of leukocyte adhesion molecules, Dr. Cronstein having elucidated how colchicine works on e-selectin, these are all well characterized, and some of the actual targets are seen by specific medications now in practice including IL-1

inhibitors, TNF-alpha inhibitors, and medications being evaluated in the clinic for RA, that may not work very well for RA, but may work for gout.

Are you aware of any anecdotal evidence for some of these particular medications in trials or in use for RA working for gouty inflammation?

DR. CUSH: I am not. As you were going into this, I was going to turn around and ask you that question. I would love to see if Kineret or a TNF inhibitor has been tried in acute gout, and, if so, I would like to know.

DR. TERKELTAUB: Dr. Cronstein has told me that I shouldn't admit to using Kineret or Enbrel for gout, that it wouldn't be seemly, but I will admit to it, and there is some anecdotal evidence for some of the biologics affecting gouty inflammation, but obviously, it hasn't been done in a controlled manner.

DR. CUSH: Would responses be as prompt?

DR. TERKELTAUB: Handfuls of patients, it is very hard to tell, but there is some evidence that some of the biologic agents might work for

gouty inflammation.

DR. CUSH: So, maybe going to Dr. Weisman's question as to how do you manage someone who is very difficult to manage, who maybe you can't give colchicine, maybe you can't give nonsteroidals, and maybe you can't even use a steroid, maybe that is yet another alternative.

DR. TERKELTAUB: I think there is room for trials, for careful trials, and again, you did a tremendous job in the review. I think that one of the issues is that I think we really are seeing more complicated patients in terms of more polyarthritis and more severe flares in the elderly and patients with renal failure and transplants, and so forth.

So, I would encourage, given that these are the patients that we have a shortage of safe medications to use, that we would at least study these patients in trials.

DR. CUSH: And I think that they should be studied because they are still a therapeutic conundrum in many situations. Their inclusion in

an acute trial, for an acute indication, I think would only tend to complicate matters for what should be a relatively straightforward trial.

It is a different matter if you want to study people who have established chronic tophaceous gout, or renal failure, or one of these very difficult kind of cases, and look for the control of acute flares in those people. That is a different kind of trial and maybe even a different kind of drug is being developed.

DR. GIBOFSKY: Dr. Hochberg.

DR. HOCHBERG: I guess maybe your thoughts on one other issue, and this sort of comes out of what Dr. Terkeltaub just said. If you have patients who can take established therapy, let's say, NSAIDs, then, following your rationale, you would say that the NSAIDs should be the comparator agent, right?

DR. CUSH: Yes.

DR. HOCHBERG: Then, if you have people who have contraindications to NSAIDs, and you want to look at a new therapy for gout which might be

appropriate in that population, you know, do you want to comment on the choice of comparators in that situation?

Also, if you had something which was an entirely new class of drugs, you know, this is not necessarily a quantum leap, but a new class of drug that might be used in this condition that hadn't been used in gout before, where would the appropriate role for a placebo control be?

DR. CUSH: To answer your last question, I think in the latter instance, you know, a new product line, a new biologic mechanism of action, one not yet tested, I think would have to be tested in a placebo population with obviously, a very liberal policy as far as how to rescue those people, so as not to subject them to unwarranted degrees of pain and misery.

I think for a nonsteroidal head to head, to use an approved nonsteroidal as your head to head is what the FDA would require. My understanding is that if you are going to go for indication, you can go against an approved drug and

go for either non-inferiority or superiority, and that would be acceptable.

In the case where nonsteroidals are contraindicated, first, I would exclude those people from a nonsteroidal trial if possible, but then if you want to include them, then, you could use either colchicine as your comparator or maybe even steroids as your comparator.

ACTH steroids, are they approved? I don't think they are.

DR. SCHIFFENBAUER: Corticosteroids have acute gout as an indication, but ACTH, not.

DR. CUSH: Oral corticosteroids?

DR. SCHIFFENBAUER: I think it just says like prednisone would be an example of that.

DR. CUSH: That is interesting because I think there is far less evidence that that is effective compared to ACTH.

DR. GIBOFSKY: Any further questions for Dr. Cush from members of the panel? If not, Dr. Cush, thank you for a superb presentation.

We will move on to a presentation at this

point from the members of the Merck Research Laboratories.

Dr. Agustin Melian will introduce his colleagues, who will make the presentation.

Dr. Melian.

Merck Research Laboratories

Introduction

DR. MELIAN: Thank you and good morning. I am Dr. Agustin Melian and I am a Director of Clinical Research at Merck Research Laboratories.

As Merck is one of the few sponsors to have recently carried out studies in acute gouty arthritis, the Agency has asked if we might come here today to share some of our experiences with the group. On behalf of Merck and Merck Research Laboratories, I would like to thank the Agency for this opportunity.

As I think the Committee is well aware of here today, acute gouty arthritis is one of the most common inflammatory arthropathies in men over the age of 40. Despite this relatively common clinical occurrence, there is a relative paucity of

data from clinical literature on acute gouty arthritis studies.

Those studies that have been done for the most part have had just a limited number of patients, many haven't included a large number of endpoints, and many haven't included a large amount of information on the endpoints that they have included.

So, the question faced by the Committee today is the same question that was faced by Merck when they first conceptualized and designed their studies, that is, in the absence of extensive clinical data, how best to conduct studies in acute gouty arthritis.

In order to try to answer this question, Merck scanned the available literature, reviewed FDA guidance documents, and then brought together experts in the field of clinical rheumatology.

Based upon the advice of these experts, we then carried out two clinical studies. They were replicate studies in acute gouty arthritis, Study 040, published in 2002, in the British Medical

Journal, and Study 049, published earlier this year in Arthritis and Rheumatism.

Here to discuss key issues from the design phase of the Merck studies is Dr. David Daikh. Dr. Daikh, along with Dr. Ralph Schumacher, was one of the key pivotal investigators who were first involved with the design and conceptualization of these studies.

After Dr. Daikh's presentation, I will return to the podium to discuss and briefly summarize the study results. Then, Dr. Daikh will present a brief presentation on Lessons Learned.

With that, I would like to turn the podium over to Dr. Daikh.

Thank you.

Design Considerations in Acute Gouty Arthritis Studies

DR. DAIKH: Good morning. I appreciate the opportunity to discuss with you and review some of our experience in setting up these trials in acute gout, and also, as a rheumatologist, appreciate the interest of the FDA in studying this

disease in more detail.

I will discuss with you design considerations in acute gouty arthritis. I think that given the previous presentations, I will just touch briefly on issues of pathophysiology as they relate to issues of study design.

I will then review briefly the extant literature that was available and that we used to guide our own design, and then really spend most of the time talking in detail about some of the considerations that, in fact, many of these were actually outlined very nicely by Dr. Schiffenbauer. I think you will see that we covered much of the same ground in these deliberations.

I will also then talk in some detail about the approach to data analysis that would be required by different study designs.

Really, after the definitive presentation on acute gout, there is nothing really I can add, certainly given the collective experience of the panel, except really to emphasize that this clearly is, as we all know, a clinical syndrome that is the

result of an immune response to monosodium urate crystals.

Really, because of the inflammatory nature of the disease and the clinical expression of that inflammation, I would argue that we are really dealing with a unique clinical entity.

The diagnostic criteria proposed by Wallace and coworkers a number of years ago have been alluded to in a number of ways, and I want to spend a couple minutes going over these specifically.

They really reflect the reality of clinical practice, that once you have some certainty of a history of crystal-induced arthritis, the diagnosis in the acute setting is greatly simplified, so the presence of characteristic urate crystals in the joint at the time of diagnosis in fluid is critically important and allows you essentially to make a diagnosis of acute gout, or indirect evidence of the presence of crystals, that is, tophi either clinically apparent or present on a radiograph.

However, it is important to emphasize that even with definitive diagnosis of crystals, either directly or indirectly, one still needs the subpoints which are, in these criteria, C1 and C4, that is, the maximal inflammation developed within one day, and that there is redness in the observed joint, really emphasizing the importance of inflammation in making this diagnosis.

In the absence of either immediate, direct or indirect evidence of crystals, further, the criteria allow a diagnosis with a number of points that have been mentioned. I am just going to emphasize them again because it makes the point that this is a stereotypical clinical response and you can make a diagnosis of acute gout on clinical grounds.

So, in addition to maximal inflammation within 24 hours, more than a history of acute attacks, mononeuritis, in particular podagra, involvement of the first MTP, unilateral involvement of the first MTP, and then the others that you see listed there.

As has been very comprehensively reviewed, we really divide our treatment of acute gout into essentially what is preventative treatment of the acute attacks and then treatment of the acute attacks. We will be for the purpose of this discussion really focusing on nonsteroidals and similar drugs, colchicine and corticosteroids.

Before we get to the details of our own study of a COX-2 specific inhibitor compared to a standard nonsteroidal in acute gout, I just want to address the issue of what quantitative studies were available at the time of our own design to assist in guidance.

Listed here are the total number of studies. Now, these are with the exception of the highlighted studies, double-blinded, controlled trials in acute gout up to the time of our own involvement in the study.

The highlighted studies have been alluded to. I am going to discuss in detail the observational study, as well as the placebo-controlled trial of colchicine. The third

highlighted study was a double-blinded, controlled trial that will be discussed subsequently as we address the issue of quantification of Indocin's effect on this disease.

But I just want to emphasize, as you look at this list, a number of points. One, it was a remarkably short list. Secondly, most of these studies have a very small number of patients, and a number of them, most of them actually are quite old. So, in fact, very little guidance as we will see in terms of prior experience with these kinds of studies.

Now, what study or studies do we have to tell us about the natural history of gout, and what I am really going to be addressing here is the issue of spontaneous resolution of disease.

Well, we have one, the observational study of Bellamy et al. in 1987, the rationale of which was really to serve as a documentation of the natural history of this disease with the express goal of potentially guiding future studies, so really what we need.

As was noted, this was a small trial of 11 patients. These were patients who presented with classic podagra or had a history of prior attacks. The measurements were, as you might expect, pain, tenderness, swelling, erythema, et cetera, but importantly, these patients were observed in an inpatient setting. They were hospitalized and observed over the course of the study.

Now, also importantly, the mean time from the onset of the patient's attack to their enrollment in the study was 2.8 days. The baseline level of pain in these patients was graded as severe or very severe, and, in fact, the mean pain at entry in study, in this group of 11 patients, was 3.73. This was on a scale of zero to 4.

Here is the data. I want to emphasize a couple of points on this graph. You see here mean pain severity versus time. Now, there is actually two plots of time here. The first x axis here is study day, but here you see this is actually the mean numbers of days since the onset of attack, so Study Day 3 really corresponds to 5 days since the

onset of attack. This will be important for us to keep these two timelines in mind as we move forward and look at this in other studies in acute gout.

You can see, then, for study days, up to Study Day 3, which corresponds to 5 days since the onset of attack, there was essentially no change in the patient's pain severity. Then, beyond 5 days into the attack, there was some diminishment of pain.

Now, as I think noted previously, 2 of the patients of the 11 dropped out during the course of the study because of unbearable pain essentially, and so this plot, also from the publication, shows an intention to treat analysis with these 2 patients included. You can see really very little difference, the conclusion remains the same.

So, from our single study, the natural history of acute gout, we would conclude that there is essentially no resolution in severe to very severe pain over the first 5 days from the onset of attack, and that really even at the point there begin to be some resolution of pain, it was minimal

over the course of 7 days. This, I think really reflects our clinical experience.

Another study that potentially can guide us in terms of understanding duration of attack and response would be the single placebo-controlled trial that was alluded to. This was also a study which included patients who presented with podagra, involvement of the first MTP, and this was a very short-term study, 48-hour study, comparing colchicine to placebo.

These are patients who had had crystal-proven gout, and they again, importantly, were observed in an inpatient setting. They were basically put at bed rest.

The pain scale here, instead of a zero to 4 scale, is 100 mm Visual Analogue Scale with 100 being the patient's expression of maximal pain. In addition, there was an overall clinical score assigned, which was a composite of pain, tenderness, swelling, and redness.

In terms of the baseline characteristics for this group of patients, their mean time from

the onset of their clinical attack to randomization was 38 hours, and their estimated mean pain, as we will see, at randomization was 60 to 70 mm on the VAS.

You can see here the entry point in these patients. Again, we have study days here, as well as the mean number of days since the onset of attack. Here again we see very little to no resolution over the first couple of days of study, 2.5 days here you see no change.

The other point to make from this placebo-controlled trial is essentially no placebo response especially immediately upon entry into the study. Remember this is days out from enrollment.

I think we can also contrast this placebo curve to the kind of placebo responses that we are used to seeing in studies of osteoarthritis and rheumatoid arthritis, it's a very small placebo response.

So, from these studies, we can at least feel assured with our conventional wisdom in clinical experience that at least moderate to

severe attacks do not resolve spontaneously within a 5 to 7 day time period, and that there really is very little placebo response in this acute disease.

Let me move now to a number of issues that could be considered, that were considered as we set up the study. Well, as has been alluded to, an important point is really control versus a comparator design, placebo versus active comparator, and if an active comparator design is chosen, what should be the comparator drug, which patients should be selected, what endpoints should be chosen to measure outcome and when should those measurements be made.

Let's consider the pros and cons of a placebo design versus active comparator. In terms of placebo control, obviously, the major major pro is that this greatly simplifies the interpretation of results.

The disadvantages, especially in acute gout, I think are numerous, and issues that we grappled with. Importantly, as has been alluded to in some of the questions, patients and referring

physicians know how painful this condition is, many of the patients have had it before, and they also know that effective therapies are readily available.

I really want to emphasize that we are dealing with both a practical approach and perhaps an ethical approach, but certainly because of the practical issues, raise the difficulty of enrolling patients, and then the question is it really ethical to withhold effective, readily available treatment in these patients with highly inflammatory, very severe pain.

In addition, not only a practical issue, but an issue that would potentially confound the data analysis is the issue of dropouts, patients who maybe were willing to enroll in the study, but then because they were receiving placebo, continued to have severe pain, dropped out during the course of the study or potentially required some rescue medication, which we can discuss.

The other issue, as I think was addressed in these prior studies, the potential need to have

patients in an inpatient setting, to monitor compliance and to prevent self-medication by patients with readily available over-the-counter medications.

If anything, remember the two studies that I reviewed. Those were inpatient studies. I think, if anything, those studies may have overemphasized the speed to resolution because those patients were not ambulatory.

Now, consider the active comparator design. The advantages or pros of this design certainly are that standard therapies, nonsteroidals, corticosteroids, perhaps to a lesser extent colchicine in the short term, are known to be highly efficacious and obviously readily available.

The ethical concerns do not apply, this is a more humane approach, giving patients therapy at the time that they need it, and this presumably would also minimize the issue of enrollment concerns, as well as dropout concerns during a short-term study.

The cons to a active comparator controlled trial are also potentially significant, that is, more complex statistical requirements.

In particular, I am going to touch on these points, the need really to demonstrate an assay sensitivity, to demonstrate that the comparator drug actually works, and, in addition, the need to assign a comparability bound, to compare the two drugs, to show that they actually are clinically comparable or equal.

As you will see, the recommendation after deliberation of all these issues really to the sponsor was that this should be an active comparator design and that the disadvantages or cons of this design really are manageable compared to those both practical and ethical that would relate to a placebo-controlled trial.

Given the recommendation for an active comparator design, what should be the comparator? It was really essentially unanimous agreement that that comparator drug should be indomethacin, 50 mg/3 times a day. This was an FDA-approved drug

for the treatment of acute gout. It really is a clinical gold standard widely used in practice and historically, the first and longest used drug.

This is actually supported by the IMS database in which, in the United States, Indocin is the most widely prescribed drug for the treatment of acute gout. You may recall from the review of the active comparator-controlled trials, this was the most common drug used in prior studies.

Now, moving to the issue of clinical endpoints. Certainly, endpoints should address key characteristics of the disease and should, to some extent, reflect the global assessment of response to therapy.

We certainly are in agreement with the point advocated earlier that by far and away, pain is the primary manifestation of this disease, should be the primary endpoint, not only in terms of ease of assessment, but importance to patients.

Secondary endpoints could be numerous, but to the extent that this an inflammatory condition and we are really looking for a response to

inflammation, secondary importance, such as joint tenderness, joint swelling, global assessments to therapy or symptoms by both patients and investigators would be appropriate.

Now, also, in terms of the issue of inflammation, the cardinal signs of inflammation. We consider the issue of erythema, and really judge that this should probably be an exploratory endpoint in this trial because of concern about the difficulty of objectively assessing erythema in a given patient, especially given that patients were likely to have a variety of skin colors and may make it difficult to assess erythema in a comparative manner.

What about patient selection, should patients have a minimum degree of pain before entering the study?

Well, there is certainly concern that patients who have mild pain may resolve more quickly than what we saw in the two trials in which patients were enrolled with moderate to very severe pain. It very likely would be the case that some

minimum degree of pain would be required in order to demonstrate a measurable response.

So, the recommendation was that patients who are enrolled in the study should have at least moderate, severe, or extreme pain at baseline enrollment.

Now, the important issue about the timing, should a maximum amount of time since the onset of the patient's symptoms be mandated in the study? Really, here, the issue is the need to balance the time required to seek medical attention versus the time where we might see spontaneous resolution.

I showed you the prior studies that I think define some of those parameters, and I think they are well within our own clinical experience, and the recommendation was specifically to require enrollment within two days, 48 hours of the onset of an attack.

What about the issue of self-medication? Obviously, nonsteroidals are widely available. Most patients have had attacks before, they know what to use, they have it available, but there was

very strong concern that prior treatment in an acute setting would confound the analysis. So, the recommendation was that no prior use of nonsteroidals or corticosteroids would be allowed for patients to be enrolled for their current attack.

Now, in terms of the issue that was raised from some of the questions, what about chronic therapy? Really, the feeling was I think as alluded to, that if a patient was on chronic prophylactic or suppressive therapy and doing well, now had a recent change in their medication, that might be the cause of the current attack or might prolong their current attack, that that would be okay.

The recommendation was that if patients were on stable allopurinol or colchicine, that they actually could be enrolled for an acute attack.

Now, in terms of timing of the assessments, certainly it is important in terms of the time that you measure the response, that that should be integrated over a clinically meaningful

time period. Certainly, in a disease like gout where we know eventually, the attack will resolve, that needs to be within a time period where we will not be seeing spontaneous resolution.

In addition, given that this is such a common disease and people are treating it regularly, it would be important to look at the assessment over a clinically meaningful or practical time period that most people are expecting a response.

Now, going back to the other end, the outside of treatment or assessment period, but what about the short end, what about measuring over a very short time period?

Well, if we had limited data in terms of the overall duration of an attack, there are even less data to guide us in short-term measurements.

There are really very little data talking about acute response to analgesics or nonsteroidals in acute gout, but there certainly was at least theoretical concern that for this highly inflammatory condition, the onset of the effect of

therapy might take longer than you would normally see in an acute pain model because of the inflammatory response, and not too much data to guide us in predicting for a given nonsteroidal when that response would occur.

So, the recommendations in terms of timing were as follows: that the primary time period for assessment would be over Study Days 2 to 5, and as I have mentioned, the feeling was that this would be within a time period where we would not expect to see spontaneous resolution.

In addition, a secondary time period would be used over Study Days 2 to 8 to capture that period which is typical for patients being treated for gout today in the clinic.

In terms of the short end or the front end of therapy, the recommendation was to collect data on pain assessment at a 4-hour time point after the initial dose of Day 1 of enrollment.

So, given this clinical background and those study design parameters, I want to just briefly discuss the issues of statistical analysis

in a study like this.

One can imagine at least theoretically two broad approaches to measuring assay sensitivity. One, we might call a clinical approach or a qualitative approach. The other would be a quantitative approach.

I think if I could state in words the qualitative approach, it would be really that if the observed response is consistent with clinical expectations, then, in a comparator design, the effect would be attributed to the treatment.

Now, this qualitative or clinical approach really requires a number of things to be in place. One is to have a comparator drug that is reliable and effective. That certainly is the case with indomethacin, the clinical gold standard for treatment as we discussed, and really, I think indomethacin has a particular response.

I think that you will see, as you see the presentation of data from this study, in fact, this was borne out in the study, in fact, did have a very predictive response.

In addition, for this clinical comparison, it would be important to be confident that gout attacks would not resolve spontaneously over the study period, and as I have shown you, we would predict that that would not occur over the five days of the study, especially if patients were starting out with moderate to severe disease.

Finally, this would require that a placebo effect be small, and as we have seen from the placebo-controlled trial, there is a small placebo effect in this disease.

On the other hand, a quantitative approach would have a number of other requirements. Unfortunately, we have about as little information to guide us in this area, as well.

A quantitative approach would really require that a boundary be established for response to the gold standard drug, indomethacin, and that would be the level of response at which indomethacin would have to exceed.

One needs for this sufficient data from the literature to determine the magnitude of

indomethacin's effect. Unfortunately, that data is very minimal, and we will see that in the next presentation.

But, in fact, there really is no precedent in the literature for establishing the minimal effect size for indomethacin or any other nonsteroidal.

So, because of these limitations, the clinical experience, the nature of the disease, the recommendations were that the clinical approach would be acceptable in an assay, a study design of this sort, but that a quantitative approach would be included as supportive information to the extent that it was supported in the literature and could be measured in the clinical study.

Once the gold standard or active drug is chosen and presumably an assay sensitivity could be ascribed, the other important point then, and requirement, would be that some boundary of difference between the active comparator and the study drug be established.

This would really be the boundaries for

the difference between indomethacin and the study drug within which those drugs must fall.

This, we felt really needed to be based on not only extrapolation from other conditions or information in the literature, but really based on something that would be clinically relevant and clinical judgment.

The recommendation here was that the boundary for effect size of the two drugs be established at 0.5 on a zero to 4-point scale. This 0.5 threshold is somewhat more stringent than the Delphi consensus, which has been established for osteoarthritis, which is 0.7 on a zero to 4-point Likert scale.

I think it is also consistent with clinical judgment about what is a clinically relevant or important degree or pain relief, and also a level that has been used in other clinical trials, for example, osteoarthritis.

Finally, then, this is just a graphical representation of what I am talking about in terms of comparability.

This just shows the mean difference over Days 2 to 5 when we would just theoretically conceptualize between two drugs, and the requirement here would be that the mean difference, as well as the 95 percent confidence intervals for study drug compared to active comparator, would have to be within the comparability bounds of 0.5.

So, I am going to conclude there with that consideration of general study issues that pertain to acute gout and those that we considered in this talk.

I will just actually summarize here for you, really, that because of our paucity of data, this is a formidable challenge, and we really based our design on information that was available, and really to emphasize as we move forward and look at the study specifically, to emphasize the key study issues that we considered.

The issue of active versus placebo controlled, the challenge that the comparator control would be manageable while those of a placebo control would not be approachable in a

clinical study.

Issues of endpoint, that is, the need to choose those that are relevant to the disease, and finally, the timing of assessments, the need to choose a period least likely to be affected by spontaneous resolution.

I am now going to turn the podium back over to Dr. Melian, who will present to you the specific experience in these studies of etoricoxib compared to indomethacin.

Experience of Etoricoxib and Indomethacin in Acute Gouty Arthritis

DR. MELIAN: Thank you, David.

Now that Dr. Daikh has reviewed key issues that went into the design of the etoricoxib versus indomethacin studies, etoricoxib being the COX-2 inhibitor that was studied in the Merck studies, I am next going to go over the study results.

As shown in this next slide, is a schematic of the study design. The recommendations of our rheumatology experts were followed in the design of this study. The study had an active

comparator design. Patients who met eligibility criteria were randomized on a 1 to 1 ratio to receive either etoricoxib 120 mg/once daily or indomethacin 50 mg/3 times a day.

For the purposes of this study, the first day of study treatment, which was also the day of randomization, was defined as Day 1.

Day 1, by definition, had to occur within 48 hours of the onset of the attack, because this was one of our inclusion criteria, so patients had up to 48 hours, if they met inclusion criteria, they were then randomized to one of these two study treatment groups.

A study timeline showing day of study and day relative to the onset of attack is shown on the bottom of this slide.

The primary efficacy hypothesis of these studies was that etoricoxib 100 mg/once daily would demonstrate clinical efficacy comparable to indomethacin 50 mg/3 times a day as assessed by the patient's assessment of pain over a 4-day period, Days 2 through 5.

A secondary hypothesis was comparability to indomethacin, the patient's assessment of pain over Days 2 through 8.

The primary and key secondary endpoints are shown here. The primary endpoint was the patient's assessment of pain. The primary endpoint was recorded on a zero to 4-point Likert scale where zero reflected none or no pain, and 4 reflected extreme pain.

The primary assessment period was Days 2 through 5. The secondary assessment period was Days 2 through 8, and there was additional assessment period on Day 1, 4 hours after the initial dose of the study medication.

Key secondary endpoints included the patient's global assessment of response to therapy, and assessment of study joint tenderness.

Additional endpoints included the investigator's assessment of study joint swelling, the proportion of patients discontinuing due to lack of efficacy, and the exploratory endpoint, proportion of patients exhibiting joint erythema.

As noted, the latter was designated as exploratory in this study over concerns that it might be difficult to detect study joint erythema in patients with distinct skin colorations. In fact, as you will see later in this presentation, that concern turned out to be unwarranted, and, in fact, erythema was detectable in the majority of patients.

The timing of the assessments during the study period are shown here. Patients, for the primary endpoint, were assessed at baseline, then again at 4 hours after initial dosing, and then once daily over a 7-day treatment period.

For the secondary and exploratory endpoints, patients were assessed on Days 2, 5, and 8. All patients had baseline measurements except for the patient's and investigator's global assessments of response to therapy since, by definition, patients needed to be on therapy in order to answer this question.

The basic selection criteria are shown in this slide here. All patients had to be randomized

within 48 hours of the onset of their attack of acute gouty arthritis. All patients had to have a clinical diagnosis of gout as defined by the Wallace criteria or the ARA criteria, which we have heard about previously.

All patients also had to have moderate, severe, or extreme pain at baseline.

Patients who took a COXIB, an NSAID, or corticosteroid before coming into the trial were excluded from randomization.

Patients who were on baseline preventive gout medications, such as colchicine or allopurinol, were allowed to come into the study as long as the dose of this therapy had been stable before they came to the study, and was not anticipated to change during the time of the study.

Basic enrollment characteristics are shown in this slide here. The first study enrolled 150 patients, and the second, 189. These are, to the best of our knowledge, the largest gout studies that have ever been performed.

In order to enroll this number of

patients, it was actually a formidable task. We used over 40 sites for each of these studies, and over 10 countries.

The main reason, in discussion with investigators, that we had difficulty recruiting patients was, in fact, that most patients self-medicate before they ever came into the clinic.

Baseline characteristics and demographics for the study are shown here. Patients who entered the study were typical of those with acute gouty arthritis. The mean age of entry was approximately 50. The majority of patients were men, and patients were of diverse racial and ethnic backgrounds.

As is typical for patients with acute gouty arthritis, the majority of patients had monoarticular disease. The most common site of arthritis in these studies was the first toe, first MTP.

Approximately 28 to 29 percent of patients in this study had polyarticular disease, suggesting

a slight bias towards patients with severe symptomatology. Consistent with this hypothesis, what we saw was that the majority of patients had severe or extreme disease.

If we looked at the average time from the onset of attack to when they entered the study, on average, patients came in within one day of the onset of their attack.

This time to onset of attack to when they were enrolled in the study presumably reflects the time required for the gout flare to flare significantly enough that patients go to see their physician, and also the logistics involved with actually getting in to see one's physician or care provider.

In the following slide are shown patient disposition. The majority of patients who enrolled in these studies continued to finish study period. There were slightly more discontinuations due both to lack of efficacy and due to adverse experiences on indomethacin compared to etoricoxib, but, in general, in both groups, the number of patients

discontinuing was low.

Shown next is the treatment effects for the primary endpoint, the patient assessment of pain. What we can see here in blue is the response amongst patients treated with indomethacin. Along the y axis is change from baseline, and along the x axis is mean days since the onset of their attack of acute gouty arthritis.

What you can see here for indomethacin is we see that most patients were, in fact, on average, enrolled at the 24-hour period since the onset of their attack, and we just what we expect in terms of the treatment effect, a rapid and marked treatment response seen within the first 24 to 48 hours.

Although one needs to be cautious when comparing data across studies, it is helpful here to compare what we saw in this study to the Bellamy study, remembering again that the Bellamy study was the observational study where patients were followed over time in the absence of treatment.

What we saw in that study is that

patients, on average, were enrolled approximately three days after the onset of their attack, and for the patient assessment of pain, they saw very little to no response out to Day 5 since the onset of their attack.

This is in marked contrast to what we saw with indomethacin in terms of effect size in this study. If we next look out over the subsequent four days, what we see is small treatment effects in the indomethacin group and small improvements also in the observational study. However, the relative magnitude of these effects compared to that seen early on with treatment with indomethacin was small.

Next, shown in yellow, is the response for the primary endpoint for etoricoxib. What we can see here is a very familiar pattern where the response for etoricoxib over Days 2 to 5, the primary assessment period of this study, Days 2 through 8, the secondary assessment period, and also on Day 1, four hours after initial dosing, was practically indistinguishable from that seen with

indomethacin. This is for the first of our two replicate studies.

If we next move on to the second of the two replicate studies, shown here on the right, we can see a very familiar pattern, once again looking almost indistinguishable from that seen in the initial study.

What this suggests to us is that gout actually in appropriately designed trials is a highly reproducible model and that with effective inhibition of cyclooxygenase, either nonselectively with indomethacin, or highly selectively with etoricoxib, you can see these marked improvements.

So, now, let's next move on to secondary and exploratory endpoints. If the scout study design is truly robust, what we would expect to see is similar effects across multiple endpoints, and that is, in fact, exactly what we can see.

What we are looking at here is results for joint tenderness and joint swelling. On the next slide, we will see patient and investigator global assessments, and we will see essentially the exact

same response that we saw with the primary endpoint, with a marked response occurring early on during treatment and maintained throughout the treatment period.

We see this again, tenderness and swelling, and on the next slide, we are looking at patient and investigator global assessments. For the patient and investigator global assessments, these are shown in a slightly different format because there was no baseline measurement for this endpoint.

So, what you are looking at here actually is the percent of patients that had a good to excellent response from either the patient's perspective for the patient global assessment of response to therapy, or the investigator's perspective for the investigator global assessment of response to therapy.

You can see that in each case, that by Day 2, the majority of patients from either the patient's or the investigator's perspective had a marked improvement in terms of response to therapy,

and that these improvements are maintained through the 8-day treatment period.

Lastly, moving on to the more objective measurement of study joint erythema, the results are shown here. What we can see here in these two replicate studies is that the majority of patients in both studies, over 90 percent had erythema at baseline.

Thus, our concerns that this endpoint might not be as easily detectable as some of the others, in fact, in appropriately selected patients, as we saw here, it turned out to be unwarranted, and although I am not showing you, we did subgroup analysis broken down by race, and what we saw there is that in each racial subgroup, approximately 90 percent or better of the patients had detectable erythema at baseline.

Then, let's look at the response over time where we can see here once again that same pattern, by Day 2, 50 percent of the patient approximately had complete resolution of their study joint erythema, and by Day 5, only 10 to 20 percent of

patients had any residual erythema detectable.

So, in summary, these results indicate that both indomethacin and etoricoxib were highly effective for the treatment of acute gouty arthritis. We saw rapid treatment effects and we saw improvements across multiple domains.

Now that we have reviewed the results of this study, let's next review the methodology. In order to have a successful study with an active comparator, as Dr. Daikh went over for us, there are two distinct criteria that need to be met.

The first is that the active comparator needs to have been shown to have performed as expected, and the second is that the test drugs needs to have been shown to be comparable or perform similarly to the active comparator.

In this study, indomethacin was chosen as the active comparator control because it was considered, based on clinical experience, to be highly reliable and thus, the appropriate standard for the treatment of gout.

So, based on the clinical approach, was

indomethacin effective, so based on clinical experience, was indomethacin effective in this study?

The answer is yes, indomethacin performed exactly as expected. There was a marked and rapid treatment effect, it was seen across multiple endpoints and multiple domains, and by Day 2, the second day of dosing, the majority of patients had a good to excellent response.

Moving next on from the clinical approach to the analytical approach, how did indomethacin perform compared to data generated in previous clinical studies? In these analyses, the analytical approach was considered secondary or supplementary because it was complicated by a number of factors.

First, was the relative paucity of data in the clinical literature on which to base effect size, and the second was the lack of any generally accepted convention on how the minimal bound for effect size should be calculated.

Despite these limitations, prespecified

criteria for the minimal bound for indomethacin effect size were derived, such that at the end of the day, there would be objective criteria to ensure that the positive control had performed well.

In order to do these analyses, the effect size bound was derived from the only study in the literature, a study of ketoprofen versus indomethacin, which provided serial data on pain, on the serial data, on the effect size, and variability obtained over the appropriate time period.

Because this study collected data on a 3-point Likert scale, and ours was a on 4-point Likert scale, this data was rescaled to a zero- to 4-point Likert scale.

We then extrapolated recommendations from previous FDA guidance on rheumatoid arthritis, which suggested that in studies lacking placebo, a test drug should maintain at least 60 percent of the active comparator effect size, and applied this general rule to the ketoprofen study, and arrived

at a minimal effect size of negative 1.46 Likert units.

We prespecified for our studies that both the point estimate and the 95 percent confidence interval for that point estimate for indomethacin needed to surpass this 1.46 Likert unit bound.

Although these analyses required substantial extrapolations, they did at least provide some objective criteria to support the subjective clinical assessment of efficacy provided in these studies.

Shown here now are the results for indomethacin compared to the 1.46 Likert unit bound. Shown on the left are the results of the first study 040, and on the right, the second study 049.

What we can see in both cases, both the point estimate and the 95 percent confidence interval for that point estimate surpassed or passed the minimal effect size calculated from the previous study.

That is whether you are using the

quantitative approach shown here or the qualitative approach which we reviewed in terms of looking at the overall data from the studies and saying did indomethacin perform as expected based on our clinical experience and our clinical interpretation.

The answer is the same, is yes, the active comparator worked in these studies.

Now, once you have established that the active comparator worked, the next question is did your test drug work comparably or similar to your active comparator, in this case being indomethacin.

In order to establish this, we followed the recommendations of our experts and used the comparability bounds of 0.5 Likert units. Once again, the 0.5 Likert units was chosen because it was smaller than the 0.7 Likert units suggested in the Delphi experiment to be a clinically meaningful difference, and it is also consistent with half the distance between adjacent points on a Likert scale, suggesting that if two values fell within this difference, on average, they would score the same

on the Likert scale.

Results here are displayed as difference between means for etoricoxib versus indomethacin. What we can see here is the point estimate in both of these studies, whether we looked either over the primary assessment period, 2 through 5 days, or 2 through 8 days, fell very close to the equivalence mark here shown by the solid line, and approximately 0.1 Likert units, and we see that both the point estimates and the 95 percent confidence intervals fall well within the 0.5 Likert unit boundaries shown by the dotted line above and below in these grafts.

So, in summary, I think the data that is generated in these studies actually demonstrates that the acute study design used in them is robust. Indomethacin performed reliably and as expected in the studies, and the endpoints are highly reproducible between studies, and results were consistent across endpoints.

In replicate studies, etoricoxib and indomethacin performed comparably based upon

predefined criteria, and putting all of this together, what it suggests is that meaningful results can be obtained in the absence of placebo.

With that, what I would like to do is now turn the podium back over the Dr. Daikh for a discussion of lessons learned.

Lessons Learned

DR. DAIKH: So, you have had a review of the issue of acute gout and we have talked about some of the general and theoretical concerns of study design, and now a review of the results from these two studies.

Let me just leave a couple comments in terms of what we did learn from the study and perhaps provide a preview of a discussion in terms of what we may talk about in the future.

Certainly, a major lesson, a major conclusion from these studies was that recruitment was very difficult. We had predicted that the difficulty with a placebo-controlled trial would be insurmountable from a practical standpoint, but, in fact, even with an active comparator-controlled

trial, recruitment was very difficult.

I think as Dr. Melian planned out, this required a number of centers around the world, and I can speak from personal experience, I was actually quite surprised. I was anticipating in a VA setting that we would have a lot of ease in getting patients.

I certainly agree with the point that we, as rheumatologists, are seeing a minority of patients, but I had very close working relationships with the docs in the ER, with the clinic docs, and obviously, in setting up the study, there was a plan to have direct communication, and even with all those efforts, it was very difficult.

Patients were just taking medications before they came in.

What about potential considerations looking forward to future studies? Well, in retrospect, looking at the reproducibility of the data even in a very short time period, it seems that it may be interesting and informative to

collect additional data pertaining to the onset of clinical signs and symptoms in acute gout. It may be beneficial to look at earlier times.

I think it would be reasonable to explore the use of pain measurements over perhaps multiple parameters and early time points, perhaps even considering the use of stop watches as has been done in some acute pain models.

It is also very reasonable to explore the use of alternative pain scales, perhaps to enhance precision in other than the zero- to 4-point Likert scale used in this study.

As you are all very familiar, a number of different measures and instruments could be used, whether they be a visual analogue or a broader numerical scale.

I think it also, looking forward, would be very useful to consider the inclusion of a functional outcome measure in a disease like acute gout, that would have a meaning both in terms of patient outcomes and also the ability to assess efficacy of a drug.

So, with that, I am going to pause, and that is the sum of our presentation in terms of experience in the study of acute gout.

I appreciate the attention.

DR. GIBOFSKY: Thank you, gentleman.

At this point, what is the Committee's pleasure, we are scheduled for a break, or we can begin our discussion of this paper and then take a break?

Discussion followed by a break seems to be the consensus of the Committee.

Dr. Anderson, you have the first question.

Discussion

DR. ANDERSON: Those studies were very nicely presented and very clearly presented. I just have a couple of short questions.

I was wondering why you used the Likert scale even though you would expect that VAS might offer more precision, and what you had investigated about that before deciding on the Likert.

The other question is about the use of least squares means, which are in all of those

plots, and it wasn't described what you adjusted for, and it sort of raises the issue of why that was necessary and whether there were rather different results for some subgroups of patients.

DR. DAIKH: I will just respond in general. I think it is a very good point that there are a number of scales that could be used, and that is what I was trying to get at with the summary slide, to open up the discussion.

We certainly did discuss the possibility of using a visual analogue, for example, but I will let Dr. Melian address this, as well, really relating to the broad experience of the sponsor in other pain models with this scale.

DR. MELIAN: We had used Likert scales in a number of other pain models, and it seemed to make sense for us to bring that forward. Also, in sort of reviewing the literature, one of the main studies we were looking back to was the Bellamy study, and in that Bellamy study, they also used the similar Likert scale for pain, so it at least gave us a good anchor to use.

We know that in some studies, VAS's are used, in other studies Likerts are used, and they generally tend to correlate fairly well. Would it have been wrong to use a VAS scale, probably not, and it might be interesting for future studies to actually VAS and Likert scales together an see how well they correlate in acute gouty arthritis.

DR. GIBOFSKY: The second question before we get to Dr. Hochberg, there was a question from Dr. Anderson about least squares.

DR. MELIAN: I am actually going to bring up Jim Bolognese, who was the statistician on this study. Jim, if you could address the question on least squares.

DR. BOLOGNESE: The study was stratified by poly or monoarticular involvement, so that was a factor in the model, and also baseline pain was a factor in the model, so the results are adjusted for those two factors in the analysis of variance model.

DR. ANDERSON: But were there rather different results?

DR. BOLOGNESE: No, the results were very consistent across those two endpoints. Interactions were not close to being significant.

DR. MELIAN: But this actually does bring up a question or an issue that was raised earlier amongst the panel with Dr. Cush's presentation, which is polyarticular versus monoarticular.

Obviously, what we did in our study was we enrolled both patient subtypes because, if not, we really wouldn't have any data on the polyarticular disease. What we saw was, in fact, there were similar results between the two active treatment groups in both groups.

DR. GIBOFSKY: Dr. Hochberg.

DR. HOCHBERG: Thank you, Dr. Gibofsky. I am only going to ask--I have several questions, but I am only going to ask one, and the one I am going to ask deals with something which was brought up during Dr. Cush's presentation, and the subsequent discussion.

You enrolled patients within one day, so patients came in, they were evaluated, and they

were randomized on the same day. So, what did you do in terms of the screening of those subjects at the time that they came in given the concerns that were raised in the presentation that you might end up enrolling people who had renal insufficiency, other laboratory abnormalities that might be relative contraindications to NSAID use?

DR. DAIKH: I will take that. Obviously, very important considerations, and once again, another way in which there was a need to balance the practical considerations of enrollment with the clinical concerns of the patients.

So, what we did specifically in the study, in anticipation that the decision would need to be made at the time of enroll and treat, or not enroll and treat, for patients who had uncontrolled hypertension, 165 and above, 95 and above, they were excluded.

From the standpoint of renal function, we issued guidelines to investigators that history of significant renal insufficiency would be a contraindication, and that was defined as greater

than 2 or a clearance of 30 or less.

Now, in terms of laboratory testing, that, of course, the ease of that varies by study site, if it was in a clinic versus a hospital setting, but if there had been no laboratory testing within the prior year that would guide the physician in terms of their ability to conclude there was significant renal involvement, mild dysplasia, et cetera, then, it was required that they obtain laboratory testing with results of CBC, creatinine before enrollment.

If there were values available for the preceding year that were reassuring, then, they could be enrolled.

DR. MELIAN: Obviously, this is one of the challenges with recruitment, and we worked very closely with sites to try to make sure that, where possible, they could turn over labs as quickly as possible.

I think Dr. Cush said one hour. Our experience is that most places can't get labs back in one hour, but some places can, so this is where

we really had the interaction with the site, worked closely with them, to try to get labs back as quickly as possible, and in terms of those patients we couldn't get labs back in time, we followed the recommendations as Dr. Daikh has described.

DR. GIBOFSKY: Thank you, Dr. Hochberg. I have put your name back on the queue for follow-up questions later.

Dr. Weisman.

DR. WEISMAN: You mentioned that there were difficulties in recruitment in spite of the fact that you chose this study design.

What were those difficulties and how do you relate them to the kinds of issues that Dr. Cush brought up earlier about theoretical difficulties in recruitment, what were the practical difficulties and did they match what Dr. Cush had mentioned earlier?

DR. MELIAN: I will let David give you firsthand experience with that, and then I can give you some of the secondary feedback we got from the investigators.

DR. DAIKH: In my experience, I think they matched very well with the concerns that Dr. Cush raised. Even in a setting where rheumatologists are actually involved in teaching other primary care physicians and interacting with them, a lot of these patients came to us from clinics and the ambulatory walk-in ER.

So, sometimes there were issues of prompt recognition of acute gout and sort of making the call quickly to us, but by far and away, in my experience, the difficulty was pretreatment. Patients had come in having already taken an NSAID, or having been given an NSAID by a doc in the box before they came to our study site.

The other extreme, and I think it actually probably pertains somewhat more to a VA site, the other extreme we would see occasionally would be the patient that actually had been holding out for 36 hours or longer before coming in, so by the time they came in were evaluated as beyond the two days.

DR. WEISMAN: They spent a couple of days in the emergency room?

[Laughter.]

DR. DAIKH: No comment.

DR. GIBOFSKY: Dr. Bathon.

DR. BATHON: Going back to the polyarticular patients, for the physical exam components, I was wondering if you could tell us how you analyzed those data. Did you develop a single chain score for swelling and tenderness and erythema, which was an average of all the joints?

Secondly, how did you identify the involved joints, was it patient report, or was it based on tenderness on the exam?

DR. MELIAN: The involved joints were essentially dependent upon whether the patient reported symptoms, and it was confirmed by the investigator that was present.

In terms of the actual scale used, it was on a Likert scale, and if I could have that scale pulled up for the swelling, I will show you exactly--

DR. BATHON: One of the problems of swelling in gout is you can have a single joint

involved and have, as you know, really widespread swelling with pitting edema, so it can sort of obscure really uninvolved joints.

DR. MELIAN: Right.

DR. DAIKH: The guidelines were specifically focusing on an index joint and measuring swelling of the joint itself. For those patients who had oligoarticular attack, then, the guideline was to pick the most severely involved joint, the most painful reported joint or most tender joint, and then from time of enrollment on down, that would be the single index joint that was assessed.

DR. GIBOFSKY: Dr. Cush.

DR. CUSH: Two things. One, was this a VA study, or were there other sites other than VA?

DR. MELIAN: We used VA sites, but we did not explicitly use VA sites. In fact, each study was performed in over 40 sites and over 10 countries each. So, we really scanned the world to get appropriate patients.

DR. CUSH: I am confused by some of the

fuzzy math that you presented. What I am confused by is you used Bellamy's paper and said that there was two days of symptoms, and you added that on to what they reported to give us some graph.

Firstoff, that was a mean of 2.8 days, and it ranged from 1 to 5 and you don't know.

DR. MELIAN: That's correct.

DR. CUSH: You shouldn't be doing that. You can only report what you know, and everything else is extrapolation. Even in your own studies, you have patient report of what happened, and I think it is misleading.

I mean it is useful information to put in the paper, but then to plot out and hazard a separate x axis just confuses matters because then later on in your presentation, you are telling us you did things on Days 2, 3, 5. I am not sure which days 2, 3, and 5 you are talking about.

So, is it the Patient Day 2, 3, 5, or is it the chronological study day? I actually know, but I am saying the ladder along the bottom needs to be gone. It sort of obscures what is true and

what you can hang your hat on.

DR. MELIAN: Obviously, if you go the paper, what we are showing is the study day. What we did here, because the purpose of this meeting is to discuss what is the natural course of acute gouty arthritis, and the best we could do was try to take an average of the data out there to try to see what it would look like, and since, on average, those patients came in 2.8 days after the onset of attack, we used that.

We can show you the data the other way. We have it the other way.

DR. CUSH: Again, it just obscures, I mean you can have a limitation to duration of symptoms at entry, and that is information. It is the same for other trials, other diseases, but then when you are reporting responses, you can't include that in your time to response, because you really don't know, and everybody's is different.

DR. DAIKH: I think that is absolutely an appropriate point, that the 2.8 days are an average. So, in fact, the data should be made more

fuzzy, that is, any defining line should have a spread around it.

I think the point that I was trying to get at in terms of general considerations in study design, I think that it is very important to pick a time within which you have got to look at the patient, and I don't think it is necessarily exactly in the 2- to 5-day period because of the uncertainty in the Bellamy paper and the absence of other papers, but I don't think it's 3 days either.

DR. GIBOFSKY: Dr. Geis.

DR. GEIS: On the Bellamy data, though, I wouldn't suggest that it really reflects what a placebo response would be.

DR. MELIAN: No, the only data we have on placebo comes from the Ahearn data, which was the colchicine comparator study, which Dr. Daikh presented.

DR. GEIS: Because in my experience, when you give a placebo in acute pain setting, you can get an enormous response, it looks like an effective drug, especially in the first few hours.

So, my question then is what was your 4-hour data? I know you referred to it, but I don't see it here. Did you ever blow it up?

DR. MELIAN: If we can put up the slide from the presentation, what you can see is that at 4 hours, there is actually pretty marked data, pretty marked response in both treatment groups. So, from the presentation, that is Slide No. 17. We are looking at indomethacin, but etoricoxib performed similarly.

At 4 hours, you see a response of approximately 1 Likert unit, and then you see a continued response over time. The largest response occurs over the initial 24 to 48 hours.

DR. GEIS: Thank you.

DR. MELIAN: I think one of the things you do see in the Ahearn paper, though, which is consistent with what is discussed in the critical literature, they are not always shown, is that the placebo response there is relatively low, and I think one of the things is when you have a disease that is driven by inflammation, particularly fairly

potent inflammation, you probably get less of a placebo response.

Do I have data to support that? Well, the only data available is that from the Ahearn paper, and that had a very little placebo response.

DR. GIBOFSKY: Thank you.

Dr. Cronstein.

DR. CRONSTEIN: Thank you. I had a question about the way you presented the data, which is the mean reduction in Likert score. I guess the problem I am having is it looks like, judging from starting with a mean score of about 3, that none of these people got complete resolution by 8 days. Is that correct?

DR. MELIAN: That is actually not correct. We actually have some data showing the degree of patients who had resolution. Well, I showed you the degree of resolution for erythema, you remember, by Day 2, approximately, 50 percent of the patients had resolution of erythema by Day 5, 80 to 90 percent, and we also have data on percent of patients who had complete resolution or had mild

to no pain.

Actually, it's very interesting. The results are practically superimposable. Whether you look at erythema or you look at percent of patients who had mild to no pain, you get these bar graphs that you could almost lay right on top of each other, suggesting that overall, these endpoint correlated extremely well.

The same thing is seen with tenderness, same thing is seen with swelling. I think what it is telling us is this really a disease that is driven by inflammation.

So, even though NSAIDs and COX-2 inhibitors have an analgesic effect, that when you look at the overall picture and you are looking at improvement, what you are seeing is all the endpoints corresponding sort of in the same pattern or in line with each other, and I think what that means is, well, yes, now you are starting to treat the inflammation, and you are seeing the effect, and the effect is across the board.

DR. CRONSTEIN: So, out of curiosity, who

are those people who didn't respond, that didn't have complete resolution? You show about 20 percent of them still didn't. Were they the polyarticular or the more severe, or did you break it down that way?

DR. MELIAN: Well, if you would look over time, the response in the polyarticular to the monoarticular is very similar, but the monoarticular has just a very smidgen is probably not--I mean I know it is not statistically significant, but the monoarticular has a very small increase in response compared to the polyarticular.

What is really interesting is the precision of the data, though, because if one looks at the treatment groups for the monoarticular, they respond almost exactly the same.

You saw how small the variability was in the study, and when you look at the two after treatment groups, the responses are almost exactly the same, and then you see the slight bump-up, or bump-up meaning slightly less response even though not statistically significantly different in the

polyarticular group with the very tight confidence intervals, it says there is probably a slight difference here with polyarticular taking a little bit longer to improve.

DR. GIBOFSKY: Gentlemen, please use the microphone, or you will be asked to make a significant contribution to the Chair's retirement fund.

Dr. Harvey.

DR. HARVEY: Actually, I would just like to say that the FDA is finding this discussion very helpful, and if I could ask the Chair if we could take a break now and then actually continue the discussion after a short break?

DR. GIBOFSKY: We have several other people in queue, I think. We will continue the discussion after the break, but I would like to give the colleagues who have been queued up, an opportunity.

Dr. Boulware.

DR. BOULWARE: My question has to do with the inclusion/exclusion criteria you used and

specifically colchicine. You, I think appropriately, excluded people who may have self-medicated themselves with COXIBs and NSAIDs and steroids, but you didn't mention colchicine.

Was that inquired and was that prevalent, and why did you not include that, too?

DR. MELIAN: Well, what we did was if a patient was on stable base like colchicine for preventive use, we allowed those patients into the study, because those patients were flaring on top of their colchicine.

They couldn't have changed their dose, though, so of the patient was on colchicine, they had a flare, and they said, oh, well, now I am going to take 2 tablets instead of 1, that patient was excluded.

Also, they weren't allowed to change their dose during the study period, so they had to stay on consistent or constant dosing throughout the study period. What we were trying to do here was really look at these drugs the way they would be used in real life, and that is the way you

typically used drugs, or at least NSAIDs or indomethacin in acute gouty arthritis.

DR. BOULWARE: But there are occasional patients who keep their colchicine at home, and they will start and self-initiate the treatment, so I guess you excluded them because their baseline was zero.

DR. MELIAN: If they started the colchicine anytime within the previous--it was 2 to 4 weeks, I would have to check exactly--4 weeks, sorry, 4 weeks, they weren't allowed into the study.

DR. GIBOFSKY: There are two colleagues in queue who we will continue now, and then we will take our break.

Dr. Hochberg with a follow-up question?

DR. HOCHBERG: If I can follow up on something which Dr. Cronstein started. The average pain when patients began in the study was severe on the 5-point Likert scale, and the average at the end of the study was mild, and we know that there are about 20 percent who don't respond with regard

to the good or excellent improvement on the global assessment of response.

So, the first question is should one look at what is really important to the patient is not that they still have mild pain, is that the pain is gone, resolution of pain as the outcome variable, and the second, which that might happen, but you don't see it often in a 7-day study, so should the study, in fact, be longer than 7 days, and maybe you can tell us what happened to these patients after 7 days.

DR. DAIKH: I agree with you in general, but again this is a balancing of a clinically meaningful time period. Maybe 9 days would be better if you get to complete resolution in 95 percent of those patients, but then you have to start worrying about the spontaneous resolution period.

Now, whether or not there should be an outcome that would be setting a threshold for a clinically meaningful degree of pain relief, that is I think a very reasonable point and worth

discussing.

In terms of whether or not the patient really--I mean obviously they would prefer to have no pain than mild pain--but I think mild pain compared to placebo would be clinically meaningful at 7 days, for example.

DR. GIBOFSKY: Dr. Hoffman.

DR. HOFFMAN: I think that the diligence with which this study was designed and carried out makes contributions beyond just setting a new standard for rigor in trials with pharmaceutical agents.

One of the things that I am wondering about in terms of your exploratory endpoint of erythema is fortuitous, that you look at it as an exploratory endpoint in part because of what a soft measurement it is, but also it raises questions about whether erythema always is part of inflammation, because we know in a variety of other situations, such as studies of wound repair, tissue regeneration and repair from trauma, that is either surgical or accidental, that we often see erythema

persist for extended periods of time even in the absence of inflammation.

So, I would compliment you on having brought that issue to further light and discussion, and I would take that as evidence for us not to include erythema as an important endpoint in looking at gout or perhaps other inflammatory conditions where indeed it may not be such an accurate marker of inflammation as opposed to tissue repair.

DR. MELIAN: I think what we heard from Dr. Cush, and obviously we took the same approach in our study, was that the primary symptom that the patient is most concerned about is pain. We did, as I mentioned, looked at erythema because it was a potential marker of inflammation.

We had the same kinds of concerns that you have. There were approximately 10 to 20 percent that by Day 5 hadn't cleared the erythema, and maybe those are the kinds of patients that you are discussing, but in the majority of patients, it did correlate extremely well with the other endpoints,

and even if it is not a primary endpoint in studies, I think it provides additional valuable information at least in the sense that if you could see that it correlates in general, not necessarily on a per-patient basis, I think that would add to one's interpretation of the data.

DR. HOFFMAN: I was speaking more to the fact that at Day 8, there was still, in the absence of significant pain, perhaps no pain, that there was still erythema, and certainly we have seen in our patients, people who still have very modest erythema that may be there for a week in the absence of any pain whatsoever. We see it in surgical wounds all the time.

DR. MELIAN: And I would concur with you, and I think even in an extremely inflammatory joint sometimes, because, if for no other reason, you have this infiltration, perhaps it has to do with wound healing, but the infiltration of inflammatory cells, and then you have got a residual.

Sometimes that erythema at the end, at least in my own personal experience, probably has

to do more with the tissue destruction and the leftover effects of that, and that is probably what you are getting to with wound healing.

DR. HOFFMAN: I was thinking more of the neovascularization that we see and when.

DR. MELIAN: I am just curious, the neovascularization of the wound healing, how quickly that occurs, so if it is an acute attack of acute gouty arthritis--

DR. GIBOFSKY: Presumably, your hand is in your pocket because you are reaching for your wallet to make the contribution for not using the microphone.

DR. MELIAN: I was just curious as to how quickly that neovascularization occurs.

DR. HOFFMAN: I can only speak to experiments done in college many years ago, where we actually saw neovascularization in the process of wound healing within a week. That is not a literature I follow anymore.

DR. GIBOFSKY: Very quick question before we break. You told us about 8 patients, 7 have an

adverse event, 1 had a laboratory adverse event.

Can you give us a little bit more detail on those 8 patients?

DR. MELIAN: I am happy to. I just want to make sure, because it doesn't have to do so much with study design. In terms of discontinuations and adverse experiences in this study, the most common adverse experiences were just those that one would expect to see with NSAID treatment, and particularly with indomethacin.

Dr. Cush actually showed in his slide our data on safety, and what you saw was that the safety features, the adverse experiences, the most common body system involved was actually the neurologic, and you saw the same sorts of CNS kind of adverse experiences that one would expect with indomethacin - dizziness, lightheadedness, these kinds of vague neurologic findings. Headaches were extremely common, and you saw a marked difference between the indomethacin group and the etoricoxib group.

Other body systems, GI was a fairly common

one. Once again, with a selective inhibitor, you saw less of that than you did with indomethacin, but overall, the number of events was low.

DR. GIBOFSKY: Thank you.

At this point, we will take our break. We will come back and resume if there is further discussion on this paper. If not, I am told that there are no individuals queued up for public comment. So, if there is no further discussion on this paper, when we come back into the regular session, we will go right into the questions that have been posed to us by the Agency.

A 15-minute break. Let's resume at 11:13.

[Break.]

DR. GIBOFSKY: You will all note that a floor mike has been put in that corner of the room, so that that will diminish the Chair's retirement fund in the event that people have to respond from other parts of the room.

We are going to resume the morning session. I would like to continue if there are further comments about the presentation this

morning, I would like to continue that discussion. I was told that the Agency found our discussion particularly useful and would like to see if there are any further comments from any other members of the panel or additional comments from the members of the panel who spoke on the presentation this morning.

Are there further comments or discussion from other members of the panel? Dr. Cush.

DR. CUSH: I would like to make I guess a pitch for Likert scale evaluations. My concern about a 10-centimeter Visual Analogue Scale, while it gives you the presumption of greater spread and ability to pick up finer degrees of change, in fact, I think that it doesn't, because most people are afraid of doing the extreme unless there they have an extreme response meaning they are totally well and they will go to zero.

Most people avoid the first centimeter or two on this end, they tend to bunch up in the middle anyway, and most Visual Analogue Scales don't have descriptors whereas, the Likert scale,

you know, on this zero to 4 scale with the descriptors, I think is much more objective and I think shows degree of change, which we can really hang our hats on.

Again, it is less sensitive to lesser degrees of change, but lesser degrees of change are not important in a disease of this magnitude. I mean I think we are looking for acute gout control where you are looking to hit a home run in every situation.

DR. GIBOFSKY: Dr. Williams.

DR. WILLIAMS: I think the data would support that either scale is equally effective, and either one can be used and show similar results.

DR. GIBOFSKY: Dr. Hochberg.

DR. HOCHBERG: Well, I guess I want to come back to the issue of outcomes, and maybe Dr. Anderson would want to comment. I don't know if you want to do this now or do this later, but in terms of whether we want to look at this as a pain model and measure improvement in pain, the way it was done in the data that were presented to us, or

whether we want to look at, you know, sort of reaching a level of no pain or reaching a level of mild pain, or a certain degree of improvement.

Thinking about what exists now is outcomes in rheumatoid arthritis trials, for example, where one can reach a state, for instance, using the DAS of low disease activity, or one can have an ACR50 improvement, something like that, whether we should I guess think about that as moving in that direction maybe for discussion with the Agency with regard to gout studies, and whether the data that were collected during the studies that were presented to us would be useful in terms or exploratory analyses in that way.

DR. GIBOFSKY: I am certainly comfortable in entertaining discussion on that now, and then we can formalize our discussion when we begin the consideration of Question 1, since that is the first question.

Dr. Anderson, would you like to comment or respond to Dr. Hochberg?

DR. ANDERSON: Yes, I like the concept of

a composite outcome, but I don't know, in an acute condition like this, I think it could be difficult, but there are two things that I would like to say on this.

One, I was impressed with the comment that Dr. Melian made about the pain response probably being driven by the inflammation response, so that this would seem not to be solely a pain situation, but there are these other components. It would seem desirable to work with more than just pain in looking at outcomes for acute gout.

The other thing, following from what you said about there now being some data that would be useful for exploring whether composite outcomes could be useful here, it may be able to distinguish between agents that you can't distinguish between when you use just pain or just inflammation or just, you know, whatever.

It is very valuable to have some good data now that somebody, I don't know who, could use to address this issue.

DR. GIBOFSKY: Dr. Cronstein.

DR. CRONSTEIN: This is more in the nature of a comment, I guess, again following up on the question that I asked before about how there seemed to be no complete resolution or many people did not achieve complete resolution of symptoms in the 8-day follow-up period.

I guess the comment would be, and this came out of some discussions with Dr. Hochberg during the break, that one, perhaps a longer follow-up should be included. I know this is getting ahead of ourselves.

I think the omission of a functional endpoint is important, and I think that that should be included, as well, because I don't think you would regain full function if you are still in the Likert scale of 1.

DR. GIBOFSKY: Dr. Mandell.

DR. MANDELL: A comment and a question. The comment is, you know, as we think about looking at markers of inflammation clinically, we have to be cognizant I think if we are picking an agent that has some specific activity against one marker

more than another, if we have, you know, something that specifically targets a molecule that vasodilates, and we pick erythema heat, we may selectively be picking one thing different, so we just need to be looking at that.

I guess in the future, we have already targeted drug therapy. We look at whether dropping a sed rate, or dropping the IL-1 specifically would be driving a composite marker of response.

I have a question for the presenters about looking at the delayed outcoming following an acute intervention. We know what the response was in terms of a secondary flare or, quote, "rebound," or anything two weeks afterwards.

Was that collected, was that standardized in a way that we can make any sense of that, and is that doable to be incorporated into an acute treatment protocol design in the future that we look for that specific question?

DR. GIBOFSKY: Dr. Daikh? Dr. Melian, would you like to respond and take either the front or the side microphone?

DR. MELIAN: In terms of following the endpoints past the 8-day period, no, we did not do that. We did collect adverse experiences after that time point, and obviously, there were some patients who would have had an adverse experience that might have been associated with gout, such as pain or gout flare or something of that sort.

We did see that in a small number of patients, but it was relatively small. Now, in terms of would it be helpful to look over that time point, it may be in future studies.

DR. GIBOFSKY: Dr. Cush.

DR. CUSH: To speak to Dr. Mandell's question, in fact, most of the acute gout trials do not look at that. It has been rarely mentioned in over 30 trials that I looked at, that there was a mention of it, but it was obviously not well studied.

It seemed to be almost an afterthought to the design of these trials, suggesting that again it was either not designed to look at that, or we don't really want to know that, and if the goal of

therapy is to control the acute attack, you can do that with the number of days to maybe a week or two, but then what happens after you stop therapy and go on is relevant to the treatment of the acute attack.

I think as Dr. Mandell suggests, that may need to be incorporated, so, you know, an acute treatment period of one week to two weeks, where the first week is full therapy, second week might be withdrawal of therapy, and then an observation period as we do in other trials certainly for safety reasons, but also for the purposes of looking at recurrence of disease, which would be yet another secondary outcome that would be important in gout.

A lot of new cases of gout will respond to just one attack, but those who have chronic gout, who have intermittent attacks, may have more attacks subsequent to this, and we need to worry about that.

Again, that could be six months from now, that could also be in the next 30 days, so I think

that to fail the next 30 days would be a serious indictment for any therapy.

DR. GIBOFSKY: The comment was made and was kind of left undiscussed or unopposed, that for short-term trials, patient-reported outcomes and health-related quality of life indicators may be less useful than for trials of a longer duration.

I would be interested in hearing how some of the members of the panel feel about that.

Ms. McBriar, would you respond, please?

MS. McBRIAR: I think I agree that it is less important when you have an acute situation, the patient is just dealing with that, not really worrying about too much else except getting rid of their pain, but as time goes on, and when it is a longer time, it starts to really impact their life, and that is when you want to measure those issues.

DR. GIBOFSKY: Dr. Cush.

DR. CUSH: I think the patient-reported outcome is the end-all here. It is the beginning of the end, and everything else is sort of interesting to the rheumatologist and the

practitioner, but, you know, patient pain, and let them decide, and then after that, I mean there are obvious impacts on quality of life here, it impacts on work, that are easily measurable and dramatic in scale when they are looked at.

You know, functional measures, we stopped them a long time ago, button tests, and 50-foot walk time, but as gout is a lower extremity disease, you know, why is that not being measured in patient with acute attacks? Just look at 50-foot walk time and resolution of that.

I think that these should be incorporated in the short-term trials. I mean the perspective of what you are looking to accomplish or analyze are a little bit different than in safety and long-term studies where you want to see maintenance of quality of life, improvement in quality of life, but again with a hyperuricemic, and I see that acutely, with an acute gout regimen where it is the control of inflammation to control pain, you will see that acutely.

DR. GIBOFSKY: Dr. Geis.

DR. GEIS: Just to comment, in my experience in doing clinical trials in other arthritides, we thought that in the acute setting, we wouldn't see changes in function and quality of life, but we collected it anyway, and surprisingly, we did see it in a matter of a couple days, we would see something happen.

So, it seemed to be useful, and when we presented it to the physicians, they thought that was good information to have.

DR. GIBOFSKY: Do you want to respond?

MS. McBRIAR: So, what you are saying is that in a couple of days, you are seeing changes in quality of life?

DR. GEIS: I am just saying in past experience, but different arthritides, and that people did not think we would see it, but we did collect it, and we did see it, and that was kind of a eye-opener as to, gee, this would be important to get more information about function and quality of life in the acute setting.

MS. McBRIAR: I think a baseline is always

important and helpful, and anything past that really depends upon the goal of the medication, what one would predict would be helpful to the patient.

I am trying to look at it like surgery, and if you have surgery, you kind of know you are going to be not functioning real well for a couple days. If you are still in that situation a week or two weeks or three weeks down the line, it becomes much more impactful.

DR. GIBOFSKY: Dr. Anderson.

DR. ANDERSON: Just to comment that if you are using functional status or health-related quality of life health status in the very short term, after only a week of treatment, the instruments would have to be specially designed because things like the HAQ refer to longer periods of time. I don't know what kinds of instruments were used in the studies that you did, Dr. Geis.

DR. GEIS: I don't recall off the top of my head, but we did use subsections of the HAQ, as well as different measures in function, and they

were exploratory, they weren't really primary or secondary endpoint, but they gave, it seemed, the physicians information which surprised them at how quickly it appeared the patients could get back to doing some normal functioning.

DR. GIBOFSKY: Dr. Schiffenbauer.

DR. SCHIFFENBAUER: I actually agree with Dr. Anderson's comment. I think in the short term, I would be surprised if function, ability to work didn't worsen. What would be surprising is if it actually remained worse after the attack of gout resolved.

I doubt that would be the case, and that might be something to look at, but I think in the short term, you are going to see such drastic changes, I am not sure what to do with them except if they persisted after the attack resolved, that might be a useful bit of information to know.

DR. GIBOFSKY: Dr. Terkeltaub.

DR. TERKELTAUB: I want to remind the panel of a general caveat, and that is that the gouty joint is not normal between attacks. Elazea

Pasqual [ph] has published that the leukocyte count is elevated.

The general caveat is that the gouty joint is not expected to be normal even after a week of an anti-inflammatory treatment. We are not eradicating synovitis, we are not eradicating tophi by giving NSAIDs or colchicine or other medications.

It is not equivalent to treating pneumonia where you are eradicating an infection that is easily treatable with an antibiotic, and this should factor into interpretation of residual symptoms and completeness really of symptoms and of function.

DR. GIBOFSKY: I think your comments also address part of what I asked earlier, which is whether we are dealing with an either/or situation and whether we are dealing with an "and" situation, and I think that is something we will get into in a few minutes.

Dr. Weisman.

DR. WEISMAN: I think you have to remember

that these instruments reflect both pain and damage, and I think what Bob is mentioning is that there is something else going on with the joint that could affect function afterwards.

But very clearly, when you relieve pain, I think that is what Dr. Geis had mentioned before, when you relieve pain with an anti-inflammatory drug, you are going to see an effect on these instruments within a week or two rather than waiting three months.

But then other factors may influence the instruments that have to do with the chronicity of the disease.

DR. GIBOFSKY: Further discussion on the presentation this morning? Are we ready to begin the first of the questions?

We are going to begin the questions. We will break for lunch. We will then come back and continue the questions. I am reminded that we do have to at least allow for the open public hearing at 1 o'clock, so that our colleagues who may be watching this live or watching it later or

following the broadcasts and the meeting are at least advised that there is the opportunity for the public hearing at the scheduled time, so that if someone shows up at 1 o'clock, we can't say sorry, the time is past, so we will have the opportunity for the open public hearing at 1 o'clock, which will interrupt whatever else we are doing.

But we will begin the questions now, we will break for lunch, and then we will come back with the open public hearing. If comments are made at that time, we will hear them, otherwise, we will resume the questions to the Committee.

So, at this point, we are ready for the discussions of the questions that were posed to us. We begin with an introductory statement.

Committee Discussion and Questions

DR. GIBOFSKY: Individuals with acute gout often experience significant pain. Although standard treatments include NSAIDs, colchicine and glucocorticoids, none of these agents have been demonstrated to be efficacious in placebo-controlled, randomized, double-blind

studies. Therefore, it is important to carefully assess any new therapy for efficacy.

I don't think this is a statement that requires much discussion, so the first question is, the first issue:

I. Please discuss whether gout is considered a unique clinical entity or a model of acute pain.

Who would like to tackle that first? Dr. Williams.

DR. WILLIAMS: I don't think any of us would treat an acute attack of gout with just analgesics, so I think that I would consider it a unique entity with which pain is a component.

DR. GIBOFSKY: I see nods. I see Dr. Cush's hand, so we will go to Dr. Cush's hand, and then those who are nodding.

DR. CUSH: Gout is a model of acute inflammatory arthritis and, hence, should be treated as a separate entity. Control the inflammation, you control the pain, yet it is, nonetheless, interesting that the use of

analgesics, ketorolac and/or topical ice have an additive effect here. The topical ice therapy was added on top of colchicine and nonsteroidal therapy, so again this should be taken into account, but it was additive in its benefits.

DR. GIBOFSKY: I might pose a question to Dr. Harvey. What are the differences in terms of our finding whether it is a unique clinical entity or a model of acute pain as opposed to finding that it is both?

DR. HARVEY: I think the purpose of the question was to stimulate discussion, and it has been effective in that.

DR. GIBOFSKY: That answers my question.

So, does anyone else want to comment on the statements that have been made thus far as to the characterization of gout? I think the consensus seems to be it is a clinical entity that causes pain, but in and of itself, it is not a model of acute pain.

Is that a fair summary? Dr. Cronstein.

DR. CRONSTEIN: Again, just based on the

discussion earlier about functional endpoints, et cetera, I think it is very clear that we don't do that for most analgesic trials, and I would just like to reiterate that this is probably something that wouldn't respond simply to analgesics, although we obviously haven't tested that.

DR. GIBOFSKY: Anyone else? Dr. Geis.

DR. GEIS: I just want to be clear I am understanding what people are saying, that even though it is not just a model of pain, and it is a separate functional entity, if it was studied like classic pain studies are done, and it was shown to be useful for understanding a drug's ability to control pain, could it be considered an acceptable pain model even though we accept that it is a different functional entity and there is all kinds of inflammation involved.

DR. GIBOFSKY: Dr. Williams.

DR. WILLIAMS: I don't think I would enter my patients into a trial with an acute attack of gout if the only treatment were analgesia.

DR. GEIS: I guess what I am saying is so,

for example, if you had an NSAID was going to be your active comparator, and you said we are going to put a placebo arm in and we are going to measure on an hourly basis from the first four hours after you see the patient, and you can rescue them out of the placebo group if nothing happens.

And you saw a separation from placebo within an hour, my experience is that is sort of considered a good pain model. If that seemed to happen with gout, why not do it?

DR. WILLIAMS: If you are using an NSAID, I think you are then confused by whether it's the anti-inflammatory effects of the NSAID or the analgesic effects of the NSAID, and I would consider that, but if you are going to tell me you are going to treat with demerol, I wouldn't be interested.

DR. GIBOFSKY: Dr. Cronstein.

DR. CRONSTEIN: I guess i just wanted to reiterate that colchicine, which is again one of the standard therapies, is not, as far as I know, particularly useful as an analgesic, and if that

were your comparator, I am not sure how you would draw any conclusions from a trial if it were set up as an analgesic trial.

DR. GIBOFSKY: Dr. Hochberg.

DR. HOCHBERG: I want to go back, I guess, to Dr. Geis's comment here then. If gout was considered a model of acute pain, you could then apply the guidance document or the draft guidance document for studies of agents in acute pain to gout, and utilize those outcomes then.

My understanding--please refresh my memory here--but these are predominantly short-term studies in acute pain, and wouldn't necessarily reflect the duration of the study and the time to response that the clinicians would be interested in, in terms of assessing the patient, or that you would necessarily expect to see the so-called, let's say moderate to excellent response if you are looking at 5 days and 7 days, right? Because my experience with the acute pain studies is that they tend to be 8 hours, 24 hours.

So, sort of by definition, I mean while it

could be a model of acute pain for the acute resolution of pain in the first 24 hours, clearly, it is more than that.

DR. GIBOFSKY: Any further discussion on point number 1? Okay, let move on to II.

II. Please comment on the use of the following clinical measures: pain intensity, pain relief, time to onset of analgesia, time to re-medication.

Are there additional endpoints that should be considered for these clinical trials, such as evidence of local inflammation, erythema, sensitivity to touch, assessment of function, patient/physician and global assessment?

Please discuss the value of an endpoint, such as time to good or excellent pain relief in a defined period of time (a responder analysis).

Dr. Weisman.

DR. WEISMAN: I don't understand the question very well. Maybe, Joel, you want to explain this? In a pain model, you look for onset, you look for magnitude, and you look for duration.

Is that what you are asking here? Okay.

The other, now you are asking about a responder index. Are you talking about a good responder, you know, a 20 percent responder? What would be an index and how would you factor those issues in, you know, an onset duration and magnitude?

DR. SCHIFFENBAUER: Well, I hate to give you a non-answer, but that is exactly what we would like the Committee to consider. The question is whether this should be studied with the acute analgesia parameters that we apply to standard acute analgesics, or is it more than that, is it that plus inflammation or other measures?

I mean what we heard in the first question was that it was a unique entity, but what I am hearing, too, is that some people would just study pain as the primary endpoint. That is the question to the Committee.

DR. WEISMAN: The message is coming through, to make it simple, no, there is more to it than the pain model.

DR. GIBOFSKY: Dr. Williams.

DR. WILLIAMS: Well, I think pain is the patient's primary concern, and probably the easiest to measure, and it would be one of your primary endpoints. The treatment of the pain is the treatment of the arthritis, and I think you would also want to study what has happened to the inflammation, the redness, the swelling, the tenderness, et cetera, and I wouldn't separate them and say we will only look at the pain. The treatment of the pain is the treatment of the arthritis.

DR. GIBOFSKY: Dr. Cush.

DR. CUSH: I will flip what Dr. Williams has said and say the treatment of the inflammation is the treatment of the pain, and so I think that inflammation measures are important in the outcome, so I still think that again the primary endpoint should always be pain as measured by the patient, using a Likert scale or PDA or Visual Analogue, I think that is all well and fine.

I do think there needs to be a

quantification of inflammation, and what is inflammation in gout? It is really the attack. In my talk, I said the attack really was the four cardinal signs of inflammation.

You could say improvement is improvement in two out of three, and the resolution is all four are gone, and that is when the attack is over, and that can be objectively measured when the patient is enrolled, when the patient comes back for their 1-day visit, their 3-day visit, their 5, their 7, whatever. That is the resolution of erythema, swelling, warmth, and tenderness in the index joint.

DR. GIBOFSKY: Dr. Bathon.

DR. BATHON: I agree that we need measures of pain and inflammation in our assessments, but I do think that it is suggested by the Merck studies, and pain may correlate extremely tightly and extremely well over the short term with measures of inflammation, which would be different from something like rheumatoid arthritis where pain doesn't necessarily correlate with the joint

findings.

If, over time, every study demonstrated a very unique tight correlation of pain with these measures of inflammation, it is conceivable that the pain could be the most important measure to assess.

DR. GIBOFSKY: Dr. Cush, to add a fifth cardinal sign of loss of function to the four previously outlined, bullet 1 asks us whether we would want to consider assessment of function in an outcome study.

Your thoughts on that?

DR. CUSH: Again, I think a secondary measure would be interesting and since most attacks are lower extremity, I would advocate a 50-foot walk time as a measure of that. Again, I did a lot of those when I started doing clinical research, and, in fact, it was kind of fun. I had a stop watch, they were walking next to the guy in the hallway, who was on his way to lunch.

But the patients themselves reported satisfaction, you could see their improvement by

doing this one test. They knew they were better by the exam or by their reports, but how they are going to do on their walk time was also an interesting exercise.

Now, there may be other measures of function one could do if it involved things other than the lower extremity, but I would advocate a 50-foot walk time or some other maybe questionnaire generated activity measure of function.

DR. GIBOFSKY: The second bullet: Please discuss the value of an endpoint such as time to good or excellent pain relief in a defined period of time.

Dr. Hochberg, can I ask for your thoughts on that?

DR. HOCHBERG: Sure, you are going to open the well here, because I will comment again on the first bullet, which I didn't do before.

I actually like the issue of achieving a certain level of response in a defined period of time, and I think that is helpful for the clinician in terms of assessing a product and giving

information to a patient saying, you know, patients like you, 50 percent will have a response over the course of a week as opposed to on average, you will have a 2-point improvement in your 4-point Likert scale.

So, I like an endpoint of time to response or the proportion of responders over a certain period of time, and think that that should probably be built in as a secondary outcome. At least the measure of pain as the primary outcome, maybe this could be modeled as a primary in terms of the improvement in pain at a certain level.

If I could have your permission to go back to the first bullet?

DR. GIBOFSKY: Please.

DR. HOCHBERG: Thank you. I am not enamored of the physician-derived measures of inflammation, erythema, tenderness here. I think I am more enamored of the patient-derived measures. Having had gout, I think the patient-derived measure here for me would be more paramount in terms of the amount of pain, the improvement in

pain, and my global assessment.

I have no objections to an assessment of function. You know, it could be both a performance-based measure and a self-report measure.

DR. GIBOFSKY: Dr. Cush.

DR. CUSH: I will pass for a second.

DR. GIBOFSKY: Dr. Anderson.

DR. ANDERSON: Do I take it, Dr. Hochberg, that inflammation can't really be measured very well, so it is not a good outcome?

DR. HOCHBERG: Well, you certainly have a lot of experience with, let's say, assessing the reliability of the measurements of inflammation, and I think while inflammation could be measured in a valid fashion, that there would need to be a lot of training in terms of getting both the inter-examiner reliability for the measurement of inflammation, be it on a, let's say, a naught to 3 scale of redness, or the so-called naught to 3 scale of swelling, and I think it is obviously much easier to do it on a present or absent scale.

I think on a present or absent scale, yes, it can be reliably measured.

DR. GIBOFSKY: Dr. Cush.

DR. CUSH: My memory has returned. I think Dr. Hochberg is right. Most of the trials, however, have looked at scores as opposed to counts on joints as opposed to dichotomous, they do want to do gradations, and ACR does have criteria for how to do that, which there is some subjectivity involved.

Marc, you had talked about patients who had responded, 50 percent of people would respond after five days. By that, do you mean a complete response, complete resolution of symptoms, or do you mean a responder index which would be some high level response involving multiple things?

I know you, as I am, you are a fan of pain, but I would call for complete resolution as reported by the patient, and maybe that can be fudged a little by saying, you know, greater than 90 percent resolution of your symptoms, and return to normal activity, but would you want a composite

measure, or would you just go with some other measure of complete response?

DR. GIBOFSKY: Response, Dr. Hochberg.

DR. HOCHBERG: Ideally, it would be a complete response. I think given what we know clinically, and given that the data that we saw this morning, which I think really inform our discussion, it would be unlikely to anticipate complete response with the sort of currently available agents within the first five days of therapy in a large percentage of patients.

So, one would need obviously a much larger study if one was going to power the study on the complete response and as a non-inferiority study.

DR. GIBOFSKY: Dr. Bathon, then Dr. Williams.

DR. BATHON: We also might want to think about whether it would be reasonable to incorporate inflammatory indices in the measure, as well, and I wondered if in the Merck study, there were any data on sed rate or CRPs.

DR. GIBOFSKY: Would Dr. Daikh or Dr.

Melian care to respond to the question of Dr. Bathon?

DR. MELIAN: No, we did not collect information on CRP or on sed rate. In clinical studies of this kind, it is often hard to get sed rate because it needs to be done locally.

DR. GIBOFSKY: Dr. Williams.

DR. WILLIAMS: My comment goes back to Dr. Hochberg's comments. I agree that I think pain is the primary endpoint, however, I do think that we can identify swelling of the joint.

I would make the comment that the committee that developed the ACR20 criteria looked at whether grading mild, moderate, severe helped, and it did not appear that those gradations helped over just presence or absence. However, if you ask for those gradations, you often got a more careful joint exam.

DR. GIBOFSKY: Dr. Hoffman.

DR. HOFFMAN: Bob Terkeltaub pointed out how abnormal the joint may be after resolution of the attack, and that emphasizes even more to me how

difficult it is to sort out the low-grade, ongoing inflammatory process from what might be a response to injury and repair, and how unrealistic it might be to expect total resolution of all of the classical features, with the most important feature then being pain and function.

It would then seem that in designing studies, that that would have to be the two absolute, most important endpoints that are included, total resolution of pain and restoration of function.

DR. GIBOFSKY: Dr. Schiffenbauer, I am going to pose this to you, are you comfortable that we have commented appropriately on the first part of the question, the use of the clinical measures of pain intensity, pain relief, time to onset, and time to re-medication?

DR. SCHIFFENBAUER: I would actually like to get some further clarification. The question is--I mean I heard pain being a primary symptom, but then inflammation being important. I didn't hear any discussion of the possibility of

co-primary endpoints. That did not come up. Some integration of pain and inflammation as co-primary, I wonder if the Committee could address that.

The second part of it was there was some discussion of time to resolution or improvement, which seems to be an end-loaded endpoint, if you will. It is an endpoint that you might look at it three or four or five, six days, but since this an acutely painful condition, I would like to hear more about the front-loaded sort of analysis, which gets back to the time to onset, those types of issues. I didn't hear that specifically being addressed.

DR. GIBOFSKY: Does everyone understand the request from us? Would anyone like to address some of those comments? Dr. Cush.

DR. CUSH: So, pain only as a primary outcome, and everything else second. Pain only and then patient reported, and everything else is secondary. I do think that everything should be front-loaded, as you suggest, and one day as your first time assessment is probably too late.

I mean I think if you are going to go for an acute gout indication, which is going to be the relief of the pain associated with acute gout, one should have a several hour determination, whether that is a 30-60-90-120 minute assessment that is done in a few trials, or whether that is a four-hour assessment as was done in the etoricoxib trial, or whether it is going to be a 6 or 12 hour assessment.

I think it should be a less than one-day assessment, and then some other intervals after that to show, and it should be front-loaded. I mean we shouldn't be looking at starting treatment 7 days and then 14 days. We have missed what is most bothersome to the patient.

What is most bothersome to the patient is how I am feeling the next 24 hours and maybe the next 36 hours, and we should have therapies that clearly show what the magnitude of response is in that time frame.

DR. SCHIFFENBAUER: How does that gibe with Dr. Williams' comment that he would not allow

an individual to be entered in a trial for demerol? Since you are just measuring acute pain, I am still not getting clarification.

DR. CUSH: They are separate issues. I mean I agree with what most people said, including Dr. Williams, that it is inflammation that is driving the pain here, and it is not pain alone, so, in an acute trial, you might get--you know, and as was seen in the ketorolac trials, in fact, they did have improvement in 30, 60, 90 minutes, but they didn't do so well after 6 hours, you know, they weren't all that great.

So, it would have to have a good blend in there because, yes, you could give narcotics to cover up pain, but have you really controlled inflammation. A lot of these would come out in the secondary variables. I still don't know that I would want to rank inflammation as a primary or covariable here, because I think it is the more difficult to measure.

We have heard some differences as to how reliable the cardinal signs of inflammation are,

whether we should do swollen joint scores on a zero to 3 scale, or just a yes and no scale. There is a lot of variation there that hasn't been well tested in this particular arena.

So, to make a secondary outcome to invite exploratory investigations, as Merck has done with erythema, just done by visual analysis as opposed to doing laser doppler studies for blood flow as a measure of erythema and inflammation could also be done.

Again, I think those are all secondary points.

DR. GIBOFSKY: Dr. Terkeltaub.

DR. TERKELTAUB: Are we going to address chronic synovitis in this setting and how to evaluate that in the trial modalities, because basically, as a tertiary care rheumatologist dealing with the worst gout, this is what is what I see. You see chronic destructive synovitis that isn't really appropriately evaluated in toto by these sorts of measures.

DR. GIBOFSKY: I think the floor is

certainly open for discussion of any parameter that the Committee considers important in the assessment of an acute or chronic trial design. We certainly can.

Dr. Cronstein.

DR. CRONSTEIN: This is going back to the front-loading, if you will. I think clearly, if you front-load everything that you are measuring and look at those earliest time points, most importantly, it is going to dictate the comparators, so if you were to compare it to glucocorticoids or to colchicine, you probably wouldn't get any change at 4 hours.

So, this is clearly going to dictate the way that you structure your trial with respect to the drug that you are comparing it to, since we have kind of written off placebo trials, and I think that that needs to be kept in mind, as well.

DR. GIBOFSKY: Dr. Weisman.

DR. WEISMAN: It seems to me from the discussion that the duration of the attack is probably not affected terribly by the medications

that we have been discussing. It is the area under the curve or the magnitude that seems to be responding, and this gets back to what Bob has been trying to tell us, that this is an ongoing process.

It is probably useful to look at it as an issue of controlling inflammation or pain as quickly and as completely as possible, but the duration of it is probably not going to affected by those specific therapies.

We all know about rebound, we all know, we use steroids, we use these drugs, if we stop them too quickly, the attack recurs. Even with ACTH, you have to give patients maintenance colchicine, so we see this from a clinical standpoint.

That probably relates again to what Bob is saying, is that the process keeps going. So, it is going to be very difficult for us, Joel, to I think make this distinction because if we are treating early and aggressively and actively, as quickly as possible, all we are going to measure is pain relief, but that is not all what is going on.

I have tried to put some kind of dressing

on this discussion in terms of pathophysiology. Maybe Bob should comment on this issue about the duration of the process, or if I am reading it correctly.

DR. TERKELTAUB: I think you read it correctly.

DR. GIBOFSKY: Dr. Williams.

DR. WILLIAMS: I am not sure I agree with that, Mike. I think that if we are talking about an acute attack of gout as opposed to patients with chronic gout, I think we do make an impact on the duration of the attack, and that we do shorten the duration.

DR. GIBOFSKY: Further comments? Does anyone want to comment on Dr. Terkeltaub's question about the assessment of chronic synovitis? I am not sure that we explored that fully yesterday, and perhaps we can revisit it.

Dr. Cronstein.

DR. CRONSTEIN: I guess the question is how long, I mean how long is chronic. I know what you are talking about as those people who have

months, but I think in terms of the sorts of questions that have been posed, for the most part, have to do with sort of life in the trenches as opposed to the tertiary care center.

I think the questions are very different at that point.

DR. GIBOFSKY: Comment, Dr. Terkeltaub?

DR. TERKELTAUB: I just want to know whether we will address the chronic patients because it is very much like RA, these types of drugs that we are discussing today, anti-inflammatory analgesics are not going to really address the chronic entrenched disease.

DR. GIBOFSKY: I think much of the discussion on chronic was yesterday, but I am certainly willing to re-explore.

DR. TERKELTAUB: There is chronic inflammatory, as well as chronic accumulation of urate. There are many people that have tophi, that don't have symptoms.

DR. GIBOFSKY: Is there some specific comments that we should be considering in our

recommendations to the Agency to take into account?

DR. TERKELTAUB: I think we should be looking at the possibility in terms of future medications evaluated in this disease, are things that may reduce the amount of destruction at the cartilage level and the amount of synovitis, and that some of these medications may not work quickly vis-a-vis pain relief.

DR. GIBOFSKY: Back to the initial characterization, Question I, that we are talking about a unique clinical disorder rather than just a painful condition, that approach?

DR. TERKELTAUB: Yes, it does, and I think we are talking about a unique form of acute and chronic disease.

DR. GIBOFSKY: Dr. Bathon.

DR. BATHON: Yes, that relates to a question I had earlier about whether you were going to base the joints that you are targeting on, patient report of pain, or the physician assessment, because the patient can see a swollen and painful hand, and it maybe is only the wrist

involved. On the physician exam, you find no involvement of the MCPs, even though there is diffuse swelling, and the patient can't necessarily separate that.

On the other end, with chronic disease, where there is acute on chronic inflammation, the physician may find tenderness in a number of joints that the patient doesn't think are involved. So, I think there are issues there that are complex and need to be sorted out.

DR. GIBOFSKY: Dr. Cush.

DR. CUSH: Well, again, we are speaking to indications, and today's indication is acute. Yesterday's indication that we spoke to was the chronic one, but was really for the indication of treating the hyperuricemia associated with gout and how treatment of that would relate to the chronic consequences of hyperuricemia and the disease.

So, it kind of gets to what Dr. Terkeltaub was bringing up, but really doesn't, and today's indication really is for the person with brand-new gout for the first time, or a person with

intercritical gout and then gets a new attack, or a person who has maybe some chronic tophaceous gout that is well controlled and has attacks, but that is a little bit different still than really a sole separate indication, which is chronic tophaceous gout and synovitis, and that would be a whole new indication that we would really have to develop, because I don't think pain would be an appropriate primary outcome there.

I think that you are really looking at more sort of rheumatoid arthritis-like outcomes where you are looking at composite measures of improvement. You are looking at synovial load, you are looking at damage, you are looking at long-term outcomes, and it may not be one regimen, it may be new therapies, it may be combinations of therapies. It really is a whole new can of worms that he has opened up by that question, and I think it is an important one because this is what we see as rheumatologists.

It is unfortunately, or fortunately for the populace, a minority of those 2.5 million

people with gout, but it is the ones that concentrate in our offices. I think today's indication is for the majority of those people who have acute presentation of gout and the intercritical exacerbations of gout.

DR. GIBOFSKY: Does everyone agree with the concept that we probably, despite two days of discussion, have not covered the universe of patients with gout, particularly those whom we may be seeing in our experience?

Dr. Terkeltaub.

DR. TERKELTAUB: Agree, and I think that as we are able to remodel the tophi in joints by more potent and more tolerated anti-hyperuricemics, we are going to start to see new types of problems with possibly accelerated destructive changes at the cartilage level, and we may have to deal with this.

DR. GIBOFSKY: Dr. Hochberg.

DR. HOCHBERG: I just wanted to get back to Dr. Schiffenbauer's comment, if that is all right.

DR. GIBOFSKY: Certainly.

DR. HOCHBERG: One can front-load the studies in patients with acute gout or acute exacerbations during intercritical gout for relief of pain as a primary outcome and improvement in inflammation as a secondary outcome, front-loading these outcomes.

It still is important to I think follow patients in study on treatment to look at the resolution of the attack where they are, quote, "back to baseline," for those who have maybe some chronic smoldering symptoms and get an exacerbation on top of it.

I am concerned that a 7-day study may not be of long enough duration for such a study if one wants to look at a secondary outcome of back to baseline or complete resolution.

DR. GIBOFSKY: Further Comments? Dr. Cush.

DR. CUSH: I would ask Dr. Hochberg and other members of the committee, would you then propose that all acute gout studies be at least 30

days in duration?

DR. GIBOFSKY: I think we will deal with that in Question III. I would ask you to hold that thought because we will come back and deal with the duration.

Further discussion on point II? Dr. Anderson.

DR. ANDERSON: I would just like to say something about function, which has sort of disappeared for the time being from our discussions. That is the difficulty in assessing whether a person has returned to baseline, because the first measurement you are going to have on people is when they are in the middle of an attack.

That is a difficulty there, I think.

DR. CUSH: But baseline status refers to their baseline, not the chronological baseline at study entry. A patient has their own perception of what their baseline function is. I was working, I was running. I think that is what the statement was referring to.

DR. ANDERSON: Okay. So, if it's patient

report of their being back to what they used to do, that's fine. I was thinking that you maybe were talking about 50-foot walk time, which you wouldn't have based on measurement.

DR. CUSH: Right. That would be a purely subjective measure of, you know, time to resolution of symptoms would be the day that the patients says I have returned to my baseline status as far as my function and my ability to function without pain, you know, plus or minus 5 percent, something like that.

DR. GIBOFSKY: If there are no further comments on Question II at this point, we will break at this point. We will resume at 1 o'clock with the opportunity for the open public hearing. We can continue the discussion on Question II following the open public hearing, which we are required to open at 1 o'clock, and then we will continue with the remainder of the questions at that time.

We will adjourn the morning session at this time.

[Whereupon, at 11:59 a.m., the proceedings were recessed, to be resumed 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

[1:03 p.m.]

DR. GIBOFSKY: Ladies and gentlemen, we are back on the record for the afternoon session.

Open Public Hearing

DR. GIBOFSKY: At this point in our schedule, we are going to hold the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. 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, 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.

Are there any members of the public who would like to present or make a statement to the Committee at this time?

[No response.]

DR. GIBOFSKY: Hearing none, we will resume our deliberations on the questions as asked.

Committee Discussion and Questions (Resumed)

DR. GIBOFSKY: I believe we have completed Question II, unless any member of the Committee would like to further comment on Question II.

Seeing none, we will move to Question III. We are waiting to move to Question III, which I will read while we are waiting for it to be put up.

Question III. Attacks of gout may be self-limited and resolve spontaneously over 1 to 2 weeks.

Then, there are three bullets.

Please discuss the duration of a trial for acute gout.

What is the value of a demonstration of efficacy within the first 8 hours? The first day?

Is there clinical meaning in an analysis of average of pain over several days? How many days?

Dr. Hochberg, can I impose upon you to begin to address Roman III?

DR. HOCHBERG: Let me start with the second bullet, and I think to summarize the way I would distill our conversation and discussion prior to the lunch break, is that there is very high value to demonstrate efficacy within the first 8 hours and within the first day. I think there was pretty much consensus on that.

Then, with regard to the clinical meaning and an analysis of the average of pain, again, I

think there was consensus that the area under the curve of pain relief was very important as well. Let's say the cumulative amount of pain relief or the less area under the curve of pain was very important, as well, measured over several days. How many days? I don't know.

In terms of the duration of the trial, while we are again interested in front-loading the assessment of efficacy, we are also concerned about the resolution of the attack, and concerned that based on the little that we know of the natural history of gout from the observational studies and the placebo group of the colchicine trial, and what we learned from the trials conducted by Merck, that either the majority of patients or a sizable minority of the patients don't have resolution of their attack by 7 days.

So, I would think that we would want to see trials of longer than 7 days in duration. I am not sure 30 days, which was the number that was thrown out, but maybe 14 days.

DR. GIBOFSKY: Dr. Cronstein.

DR. CRONSTEIN: I guess I have a question about the use of the area under the curve, and I am not sure how much value that adds to what you already saw, particularly inasmuch as the comparators are probably going to be very similar to the drugs under study just because we have already ruled out, if you will, a placebo trial.

So, it is very likely that you are going to see overlapping curves, and I don't know how much difference that--I mean not to exclude it, it's no big deal obviously to calculate that sort of thing, but I don't know how much it adds.

DR. GIBOFSKY: Dr. Williams.

DR. WILLIAMS: I actually like Marc's suggestion of 14 days. I think in the interest of patients who are feeling much better after a week, I would think that the Merck model of one today for seven days would be good, and then every other day for another week, but I would like to see a couple of weekly followups afterwards, just to make sure we have captured the full effect, and not seen any rebound.

DR. GIBOFSKY: So, I am hearing a sense that there may be difference between the period of time that the trial is conducted and the period of time that data is collected following the trial in order to get a more longitudinal picture of the natural history of the event and the treatment of event.

Dr. Cronstein.

DR. CRONSTEIN: I guess also since none of the agents got back to zero, if you will, at the 8-day time point, it seems obvious to me that you would want to get to a point where the patients are back to their baseline, if you will.

DR. GIBOFSKY: Dr. Weisman.

DR. WEISMAN: It occurred to me that I am sure Merck would have been happy to collect additional data for, say, the second week, but the problem is we are not listening to what they were saying to us, which is this was a very difficult trial to carry out. They had to go to how many countries to do this--10 in one, 11 in the other--to recruit patients in the trial with a huge

variety of different sites, I am sure, not just rheumatologists.

How many rheumatology versus non-rheumatology sites did you go to? So, half their sites were non-rheumatologists. So, we heard that they went to 10 or 11 different countries, 40 different sites, half the sites were non-rheumatologists, and many of them, I am sure, were not sites that normally do clinical trials.

So, there is going to be a huge variety of data that is collected, very difficult to put this trial together, and so I think we ought to understand that before we come up with these kind of ideal frameworks.

To do a trial of acute gout, for example, can a trial of acute gout be done in the United States? With the sites that we have in the United States, given the disease, can we do that here? Why don't we ask Merck to answer the question, can we actually do that trial in the United States with a sufficient N, not you, Dr. Cush, I want to ask Merck.

DR. GIBOFSKY: I will allow you to ask Merck if the representative will go to the microphone. At the microphone if you care to answer.

DR. WEISMAN: Given what you have told us already and given the number of patients that you need for a comparator trial to another agent, can you successfully accomplish a study in the United States?

DR. MELIAN: In the United States alone?

DR. WEISMAN: Yes.

DR. MELIAN: I think you could do it, but I think you are going to have to work very hard to do it.

DR. WEISMAN: Well, you obviously chose not to do it alone in the United States, right?

DR. MELIAN: That is correct.

DR. WEISMAN: And the reason you chose not to do it in the United States alone?

DR. MELIAN: How many years did we want to take to enroll the trial.

DR. WEISMAN: Okay, so that's the answer.

So, what I am saying is let's be realistic about the number of patients that you need to do the study, and the number of investigators that you can get, and the fact that Dr. Cush is pushing very hard on the microphone over there because he is going to reject pretty much everything that I have said.

Go ahead, Jack.

DR. GIBOFSKY: Not everything, Dr. Weisman, just all of it.

Dr. Cush.

DR. CUSH: Dr. Weisman is right. I think that it is difficult, but, you know, so is recruiting for rheumatoid arthritis in this era when we have many successful therapies currently available. To recruit for rheumatoid arthritis trials for drugs in development in 1980s and 1990s was relatively easy because there were a lot of patients, and a lot of them were not well treated, and there weren't a lot of good therapies.

Now, we have a situation where we have a lot of effective therapies, much like the situation

of gout, where there are a lot of effective therapies, and people seem to think that they know what they want to do.

But the fact still remains is that there are millions of people, that there are no trials. The main reason why this has been difficult is because we haven't had the outcomes outlined, there have been no methodology. There has not been a significant push to have the gout trials.

All the trials that we saw in development were done by interested individuals trying to answer a question, as much as there were industries trying to look at a pile of studies, whether, you know, etoricoxib or Rofecoxib or sulindac might possibly work, or might be an indication.

So, again, I think with guidelines for outcomes, with education, I mean there are plenty of researchers. It takes work, and it can be done, but to say it can't be done, I mean then we have just wasted this whole day. We have laid the groundwork where this can be done, and the patients are there.

If Merck couldn't find them, that is Merck's fault. I think that there are a lot of people who can find them.

DR. GIBOFSKY: A quick response, Dr. Weisman?

DR. WEISMAN: My rebuttal, very quickly, is that true true and unrelated, Jack, yes, rheumatoid arthritis is difficult to recruit for because we have many effective therapies. That is not true for acute gout.

We have heard we don't have many effective therapies here, as much as you think, otherwise, they wouldn't be doing the study, and the problem here is recruitment of physicians and patients in the United States because of exactly what you said this morning. It's the scattered number of patients that are out there, that are seen in emergency rooms and primary care offices, not seen with rheumatologists. They are almost impossible to capture.

I think that is the real reason, and that is why I am trying to be realistic. That is not

going to change very much, and that is why I am saying let's be realistic about study design because who is going to be doing the studies.

DR. GIBOFSKY: Dr. Cronstein.

DR. CRONSTEIN: I think again we need to query the people who have done this study and have had the difficulty in recruitments, and according to what they told us earlier, the major difficulty was that people were taking over-the-counter nonsteroidals or some other nonsteroidals that they had, so adding onto a trial where you have patients simply come back for over a longer period of time, I don't think is going to add to the burden, but maybe we could get that information from you guys.

DR. GIBOFSKY: I would share Dr. Cronstein's comments in that recognizing the difficulties in recruitment, once the patient is recruited, I am not sure the period of observation is as significant or raises additional difficulties beyond the recruitment.

Certainly, there is some, there will be some dropoff, but if the problem is in the

recruitment, that is at the front-load stage, but once the patient is there, the observation is less difficult to do.

If our colleague from Merck would care to comment?

DR. MELIAN: I agree with you. Once you have the patients in the trial, the major hurdle has been handled. Yes, you have some patients who discontinue throughout the trial, and we actually went through that number when I showed you my slides and a small number of patients in both treatment groups discontinued during the 8-day period.

You can imagine if you went to 14 days, that it would be larger yet. That being said, the major hurdle is in the first few days of recruitment.

Now, the one thing that I do have to tell you, because I am not sure it came through in my presentation, is that when we looked at patients in terms of pain, and if the system was set up I could show you, because I actually do that this data, and

I can share it with anybody who wants to see it, 90-plus percent of patients at the end of the 8-day period had mild or no pain.

So, you are really get down to what is really minimal or no pain in that 8-day time frame. I think that is consistent because when we treat gout with Indocin, we don't usually go much beyond an 8-day treatment period. Some patients do require longer.

DR. GIBOFSKY: Dr. Finley.

DR. FINLEY: I wanted to follow up kind of where we left the discussion before the break, and it dovetails with our discussion about recruitment that Dr. Weisman brought up.

I wondered, thinking about the work that the folks at Merck did, are we really talking about acute gout, or are we talking about acute episodes of intercritical gout, which is kind of where we left the discussion, and thinking about their particular studies, they talked about the Wallace criteria, and they talked about--I think I heard during the presentation about all the patients met

the clinical criteria, and I wondered if they knew, of the patients that they entered, how many were the first episode of gout that they had ever had, or were the preponderance intercritical patients.

Then, how many of them were diagnosed based on chart review of prior evidence of crystals, or, in fact, were diagnosed at the time the crystals were identified at the time of enrollment, or were the preponderance of their entrants mostly meeting the other criteria, the 6 of 12, because that has implications, as Dr. Weisman has talked about, for recruitment, and in the real world, where are we going to do these things.

Because we under these criteria as rheumatologists, but my concern really is, as has been mentioned, that we are going to create a paradigm that no one could get through.

DR. GIBOFSKY: Is that data available that can be shared in terms of first attack versus intercritical?

DR. MELIAN: Yes. Now that I am becoming

an expert at microphonetology here, in terms of first attacks, they were relatively rare in our studies, 92, 93 percent, somewhere in the 90s, 92 percent range of patients had had previous attacks of gout.

On average, most patients had 4 or greater, or at least if you categorized in different categories of how many attacks you had, the majority fell under 4 or greater.

In terms of how many had crystals, in our study, about 25 percent had documented crystals. We did not require that patients had to have documented crystals in our study. We used the ARA or the Wallace criteria.

DR. GIBOFSKY: Follow-up, Dr. Finley?

DR. FINLEY: I would just ask, as you had more and more difficulty recruiting, were you doing more arthrocentesis to document or you mentioned just there at the end that you were using the clinical criteria more, but I just want to better understand your answer.

DR. MELIAN: So, in our studies, what we

required is that they use the clinical criteria, and we set that up per the ARA guidelines. If you go through those actual clinical criteria, A and B of those criteria are crystal-proven gout. C, which is the 6 out of 12, is the additional clinical criteria.

So, we kept the rules the same, and what we got out at the end of the study were the numbers that you saw. We did not undergo any protocol changes to help recruitment in this regard.

DR. GIBOFSKY: Dr. Bathon.

DR. BATHON: One of the things I think Dr. Finley is getting at, and a concern I have, is if you extend the time point out too long, make the study too long, is that you are passing the acute gout and entering the gray area of where recurrent gout occurs, and it may be unfair to a sponsor to hold them to a longer time point when we are treating acute gout, because there is really a gray area there, who is going to have an acute attack within the next two weeks versus the next six months.

So, I think while we all are interested biologically in how long we exactly have to treat and how long that treatment is good for, I think we have to be cognizant of the fact that these are acute gout trials, and not chronic gout, and we have to make some kind of, albeit it arbitrary, timeline as to where the end of acute gout is.

DR. GIBOFSKY: Ms. McBriar.

MS. McBRIAR: I think also for the patient's perspective, they don't want to be tested and tested and tested too often either, so we need to do what we have to do to get good results, but I don't think we need to go overboard because we want to learn more.

DR. GIBOFSKY: I think we have discussed the first bullet and probably the second. The third one is a bit more technical.

Is there clinical meaning in an analysis of average of pain over several days? I guess, if so, how many days?

Thoughts or suggestions on that specific bullet? Dr. Cush.

DR. CUSH: Again, it goes to the early debate on area under the curve, more of how much time patients spend in pain. I don't think the subtleties of pain involved here require this type of presentation of data. I think it is no more valuable than the patient-derived Likert scales of pain or VAS. I think it is going to be the same thing, and again, an average over time.

I think I would rather see a magnitude or an absolute, so the magnitude is what your pain is and what is has fallen to, and then the absolute being time to resolution of pain.

DR. GIBOFSKY: Any further comments on Roman III or any of the sub-bullets? Dr. Anderson.

DR. ANDERSON: On the area under the curve, the advantage that I see is that it is a single test. The way that the pain seems to go with treatment for acute gout is that there is an initial improvement, and then the improvement continues, so that if you do an area under the curve, you are capturing the speed with which the pain is reduced and the eventual amount that it is

reduced, as well, and you are doing a single test for it.

So, that, I would think would be the advantage of it.

DR. GIBOFSKY: Dr. Schiffenbauer.

DR. SCHIFFENBAUER: Could I just get clarification? In using the area under the curve, is there any implication if the trial is a non-inferiority versus a superiority to placebo in this instance where the disease, the acute flare resolves spontaneously, would that tend to make the two drugs look more similar? You see my question there in that regard? Am I not making that clear? No?

DR. GIBOFSKY: The question is if you use the AUC, does it make a difference whether you use a non-inferiority versus a superiority.

Dr. Hochberg.

DR. HOCHBERG: I think I understand your question, and in order to have spontaneous resolution, let's say, in a superiority trial to placebo, where you would worry about this occurring

in the placebo group, you would probably have to have a 30-day trial, and then look at sort of the area under the curve for 30 days, or at least the outcome at 30 days. So, I don't think it would be a problem in a 7-day or even a 14-day trial.

DR. GIBOFSKY: Further discussion on that topic? Dr. Cronstein.

DR. CRONSTEIN: Again, I guess we come back to the comparator drugs, as well, because of the onset of action. I guess I am having a little trouble seeing the extra value aside from the fact that it's easier to compare one number to another number as opposed to comparing eight numbers or however many measurements.

So, again, all of the graphs that we have seen have been pretty much superimposable, and I imagine that going forward, since presumably, most of the comparisons are going to be made to other nonsteroidals, that, again, the graphs should be pretty much overlapping unless you guys decide to go test something different, you know, colchicine or something.

DR. GIBOFSKY: Dr. Bathon.

DR. BATHON: Unless there is a drug that can work faster than indomethacin. I mean I think the area under the curve is useful for speed, speed of response, but indomethacin works fairly quickly.

DR. CRONSTEIN: Right, and steroids don't, so I don't know that it tells you--I mean steroids may get you deeper at your second measurement than indomethacin, I don't know that for a fact, but they certainly don't do anything at early time points.

DR. GIBOFSKY: So, if you use the area under the curve, it may be a function both of the methodology and the comparator.

DR. CRONSTEIN: Right.

DR. GIBOFSKY: Dr. Hochberg. Withdrawn by Dr. Hochberg.

Any further comments on this point? Dr. Schiffenbauer, have you gotten the information, the results of our wisdom? Okay.

Let's move to Roman IV.

The onset and duration of an acute attack

is unpredictable and the extent of pain during an acute attack of gout is variable.

Please discuss the clinical trial implications of enrollment of patients who have already had symptoms of an acute attack for a period of time, for example, 48 hours.

Please discuss the clinical trial implications of enrolling patients who may be untreated or partially treated.

Shall we deal with the second bullet first since I think we have already discussed some of that earlier? Would someone care to respond to that? Dr. Cush.

DR. CUSH: I believe that the Merck approach was an intelligent one to allow patients on chronic therapy, chronic maintenance therapy with allopurinol and colchicine to continue on those therapies. I do think that there would be confounding factors involved if they were to include patients who were previously treated with corticosteroids or nonsteroidals, especially in the last four weeks.

I think that their guidelines and operations make the most amount of sense as far as enrollment criteria and allowing patients to easily enter the trial without complication.

DR. GIBOFSKY: So, you are differentiating between the patient who is on chronic maintenance and the patient who might have taken an OTC within a day of enrolling in the trial.

DR. CUSH: Chronic maintenance is okay again for colchicine and allopurinol. Any chronic use of nonsteroidals or steroids would be an exclusion, and then intermittent or recent use of colchicine or allopurinol--I am not sure how that factors in--but colchicine especially would be a contraindication to inclusion.

DR. GIBOFSKY: DR. Weisman.

DR. WEISMAN: I think this is entirely a practical issue as we heard from Merck, is that they were only able to capture patients under these circumstances. They found too many patients that had already started on these anti-inflammatory agents at the beginning of their acute attack,

which had to be excluded.

Everybody else, depending on their level of disease activity, was included, which is the same thing we do with rheumatoid arthritis. It depends on what level of disease activity they are going into the trial. So, I think it is just a practical issue.

DR. GIBOFSKY: Dr. Bathon.

DR. BATHON: One thing that might make enrollment easier is to allow patients who have taken a dose of ibuprofen, but not in the last 8 hours, because that is probably the most commonly used OTC NSAID, and it is relatively short acting, so if you had an 8-hour gap, it seems to me like that might be a reasonable patient that you could still enroll.

DR. GIBOFSKY: Anything further on bullet 2?

Let's go back to bullet 1. The implications of enrollment of patients who have already had symptoms of an acute attack for a period of time, presumably untreated during that

period of time.

I assume that is what you are looking for, Dr. Schiffenbauer.

Any comments about this? Dr. Cush.

DR. CUSH: I think in a sense there is a natural selection here. Patients will present or won't present. They are not going to present because they have dealt with this before, they have a means of dealing with it now, so they are not going to show up. They are only going to show up when things don't get better after they self-treated themselves, in which case they are excluded from these kind of trials anyway.

But the vast majority of people who have acute gouty attacks, who will then seek help, will do so within the first 24 to 48 hours anyway, so I think that that is reasonable.

Most of the trials that we looked at, that I reviewed, would include patients for either 18 hours or 24 hours, or as long as even 3 days, 48 and even 3 days, but I think that the 48-hour time limit is probably reasonable, because you want to

give the patient an ample opportunity to respond, and not catch them at the tail end of their symptoms.

But we learned I think from the way that Merck was trying to represent the data, that there was a lead-in period that they weren't truly capturing in the time it took them to get better anyway, which was, you know, again 5 days or so, certainly in their 7-day study.

So, again, you would like to get them as soon as you can, so they are going to be at their peak when you treat them.

DR. GIBOFSKY: And you would establish an arbitrary cutoff of, say, 48 hours. A patient who is untreated for longer might be less likely to show clinical effect because we know by Day 5 to Day 7, there is already some amelioration of symptoms.

DR. CUSH: Well, as in other disease, how early is early? I like it early as possible, 48 hours is very good, 36 I think would even be acceptable, but beyond 36, you are starting to get

into an area where symptoms might begin to improve.

The Bellamy study really showed that patients didn't show any evidence of improvement until after the 48-hour time period, that symptoms really began to improve significantly by Day 3 to 5. Of course, that is recognizing that is 3 to 5 plus the 2.8 days they had for time to presentation, so again, I say that up to even 3 days, you might even be safe, but 48 hours would be ideal.

Hence, if there are issues of enrollment, then, maybe allowing up to 72 hours might be reasonable as a start point in a study.

DR. GIBOFSKY: Dr. Williams.

DR. WILLIAMS: Actually, Jack covered it right at the end there. I was going to say that 48 hours, I agree most of the patients will come within that time anyway, but I don't know that there is a real--it is an arbitrary time point, and there is not a lot of difference between 48 and 72, and I would have made it 72 hours because it would make it easier for recruitment.

DR. GIBOFSKY: Dr. Hochberg.

DR. HOCHBERG: I think this may point us to one of the reasons that the company had a problem enrolling this trial in the U.S., and maybe I am completely off base and you will tell me, but a lot of patients with gout, who are followed by primary care doctors, let alone rheumatologists, have a bottle of indomethacin at home in their medicine cabinet and have been told, and may know from experience, that if they get an attack of gout on the background of colchicine or allopurinol or whatever, that they pop their indomethacin, and they may do that before they call the doctor or come into the office, which would exclude them from participating in a trial as we are designing it and as the sponsor had designed it, because they have been treated or partially treated.

So, the duration of the attack is one thing, but the fact that NSAIDs are prescribed, NSAIDs were available over the counter, and it is certainly true in other countries where you can go and buy them even without a prescription, that

people who have had gout and have been treated for gout, are likely to self-medicate themselves before they come in.

DR. GIBOFSKY: Dr. Cronstein.

DR. CRONSTEIN: Again, I would like to go back and revisit Dr. Bathon's statement at the end of the last bullet about possibly admitting people to trials who were taking the short-taking nonsteroidal, but hadn't taken it for, say, 8 hours.

Forget about the indomethacin, but many patients will just go to the drugstore and buy Motrin or Advil or something. I think that might improve recruitment. I don't know if you have the numbers as to what drugs people were taking. Is it broken down into over the counter versus prescription nonsteroidals? In the screen?

DR. GIBOFSKY: Response if you have it.

DR. MELIAN: We don't have that information with us, sorry.

DR. CRONSTEIN: But I think that is an excellent idea of permitting--and that may

alleviate some of the problems with recruitment if you permit short-acting nonsteroidals outside of a certain time frame.

DR. GIBOFSKY: Dr. Bathon.

DR. BATHON: When I look at Merck's data on the time of onset to randomization, 80 percent of the people presented within the first day, and only 20 percent within the second 24-hour period, so extending it to 72 hours is probably not going to pick up a great deal of additional patients.

DR. GIBOFSKY: Further discussion on Roman Numeral IV? Have we reached consensus, now recommendations? Okay.

Let's move to Roman V.

Considering the extent of pain and duration of attacks at trial entrance, please discuss the advantages and disadvantages of placebo-controlled studies versus active-controlled trials. If placebo-controlled studies are not recommended, are there data from studies of existing therapies sufficient to define a margin of non-inferiority?

I think we heard in Dr. Daikh's presentation, I believe there were two slides looking at the advantages and disadvantages of placebo-controlled studies versus active-controlled trials, and I think certainly that is worthy of note to the answer or to the comment on the first sentence.

Dr. Williams?

DR. WILLIAMS: I am a big believer in placebo-controlled trials, but in this case, I realize these treatments haven't been demonstrated in randomized, controlled trials, but we certainly feel that they are effective treatments, and I think a placebo-controlled trial would be very difficult to sell to the investigators, as well as to the patients.

DR. GIBOFSKY: Any other comments? Dr. Bathon.

DR BATHON: I agree with that. The other complication is that a lot of times we don't know these people. You can talk rheumatoid arthritis patients into a placebo-controlled trial as long as

there is rescue, and you could argue that maybe you could ask them to put up with--the gout patients to put up with two days of placebo, and then have a rescue, but because you don't have a relationship with these people and they are coming in desperately for treatment, I think it would be a very difficult sell to give a placebo.

DR. GIBOFSKY: I'm getting a sense that in this particular situation, we are not recommending or at least we think that placebo-controlled trials would be disadvantageous to the patient.

So, we can go to the second comment, the second sentence, which is are there data from studies of existing therapies sufficient to define a margin of non-inferiority for an active comparator.

Dr. Cush.

DR. CUSH: I wanted to add one caveat to placebo-controlled trials, which was brought up earlier by Dr. Hochberg, and that it is appropriate for truly new compounds and novel compounds for which an active comparator may not be a reasonable

comparator, I mean one that is currently approved and marketed. So, that is the one caveat.

DR. GIBOFSKY: Dr. Harvey.

DR. HARVEY: Before you moved on, I didn't know if you wanted there to be any further discussion or any elaboration on the concept of medication rescue, some of the variations on that theme.

DR. GIBOFSKY: Dr. Cush.

DR. CUSH: Certainly, a placebo-controlled trial, that would be the only way one could do that, and I think that any out point where the patient felt that the pain was extreme and unbearable, and patients have to be told that, you know, there is a chance that your condition could get better by doing nothing and just resting.

You could have as a part of placebo management, ice and whatnot, but anyway, they still have to be told they could get worse, too, and should they get worse, they could be offered either an analgesic or a standard of care as rescue therapy, and that becomes one of your arms, one of

your outcomes, your secondary outcomes.

DR. GIBOFSKY: In rheumatoid arthritis, we are learning that leaving a patient untreated for even a brief period of time may affect the ultimate outcome in the clinical course of a disease.

Do we have any data that is either similar or distinct in gout, whether leaving a patient untreated for gout in the context of placebo-controlled trial may be acceptable in the short term, but may have implications for either other manifestations, hyperuricemia, if present, or their chronic intercritical gout?

Dr. Weisman.

DR. WEISMAN: Well, we heard from Bob Terkeltaub earlier today that there is data indicating that the process continues, and there are many patients that go on with some kind of smoldering disease, just even keeping aside the concept of hyperuricemia, just the fact that the joint disease appears to progress clinically even in the intercritical periods.

Although you are not going to be able to

support this with MRI data, like you can--or early erosion data in rheumatoid arthritis, because there hasn't been any studies looking at this structural damage issue, but I suspect there probably will be at some point, there will be some data to document this whether it's investigator initiated or pharmaceutical company initiated, but there will be some data.

DR. GIBOFSKY: Dr. Williams.

DR. WILLIAMS: I think that because we are convinced we have effective therapies, that if you had a placebo-controlled trial with rescue, you would end up without a placebo control.

DR. GIBOFSKY: Are there data from studies of existing therapies sufficient to define a margin of non-inferiority?

Anyone want to tackle that one? I think we heard some of that in Dr. Daikh's presentation as to why the study was designed the way it was given the limitations of existing therapies and the ability to define the margin of non-inferiority, but anyone else want to comment on that?

[No response.]

DR. GIBOFSKY: Okay. Dr. Harvey, are you comfortable with a response to your question about rescue?

DR. HARVEY: I am never comfortable, but I will--

DR. GIBOFSKY: Would you like a cushion?

DR. HARVEY: Dr. Schiffenbauer has an elaboration.

DR. SCHIFFENBAUER: I didn't have a specific issue about the rescue, but I just wanted to get some clarification from the Committee.

If I have heard you correctly, you would allow individuals to have an attack for 48 up to possibly 72 hours, and I heard maybe some disagreement as to whether they could or could not take some therapy during that time, possibly ibuprofen possibly, or nothing, and then you were objecting or you were concerned about placebo-controlled trials, and I am not quite comfortable that I understand the difference there.

I guess the concern I have or the question

I have is if someone is untreated for 48 to 72 hours, if that is what we are saying is one way to approach this, is there an objection to entering them into a placebo-controlled trial that may continue for an additional 6 or 8, 12, 24 hours of that placebo-controlled period to evaluate in a rigorous fashion the effects of a new therapy.

DR. GIBOFSKY: So, your question is if someone has gone for two days on their own for whatever reason, perhaps it's Friday night and they can't get to their doctor until Monday, what is the up side and down side to beginning the clock at T zero and then putting them into a placebo-controlled trial.

DR. SCHIFFENBAUER: Yes, and let me just add although I think we do all think that Indocin works effectively, I don't know that we truly have any idea of when it starts to work, how effective it really is, because we don't have those placebo-controlled trials to document that. Maybe someone could address that.

DR. GIBOFSKY: Dr. Hochberg, did I see

your hand going for the microphone? I do now.

DR. HOCHBERG: Again, if we go back to Question I, I guess we felt that gout was an acutely painful condition, but it was more than just pain. You know, there was a tremendous role for inflammation.

Then, in one of the subsequent questions, I don't remember whether it was II or III, that we are front-loading the outcomes and looking at some of the outcomes that are used to assess agents for the treatment of acute pain.

So, clearly, there is a period in which this could be placebo-controlled in order to define the time course of the response in comparison to placebo in this painful inflammatory condition.

But then you get into the issue in a placebo-controlled study of rescue, and personally, I mean I have had a lot of experience in osteoarthritis trials, and I don't like rescue because I think it sort of muddies the interpretation of the results, and some of the meta-analyses now suggest that the effect size that

is seen with treatment in studies that do not allow rescue is larger than the effect size which is seen in studies which do allow rescue, suggesting that there is an effective rescue.

Then, you have to decide, well, what is the rescue going to be, does the patient stay in the study and continue to get observed on rescue to contribute to the analysis in the placebo group, or once they go on rescue, are they a failure, and then you are looking at time to failure as an outcome. So, that gets real problematic from my point of view.

DR. GIBOFSKY: Dr. Williams.

DR. WILLIAMS: Your question about how quickly things seem to respond, the data that was presented to us by Merck would suggest that they respond to both agents within the first few hours, and I find that there will be some moral dilemma to try and put patients on placebo if I can make them better. Patients with gout are miserable, and to ask them to hold off for treatment for 12 to 24 hours, I would find it a difficult ethical issue.

DR. GIBOFSKY: Dr. Schiffenbauer.

DR. SCHIFFENBAUER: Again, that is in the context of recruiting individuals that have gone already 48 hours or up to 72 hours without therapy. That is the point I want to clarify.

DR. WILLIAMS: They didn't come to me in the first 48 hours. Once they have come to me, they are then there to be treated, and that is when my time clock started.

DR. GIBOFSKY: Does that answer your question, Dr. Schiffenbauer? Okay.

Ms. McBriar.

MS. McBRIAR: It seems that a lot of people have talked about the severe inflammation that is going along with the severe pain in these patients early on, and it just worries me if the rheumatoid arthritis data is true about the early damage, and we want to preserve joints and we want to preserve function, that if we do a placebo-controlled trial, that there could be this damage to the joints early on, and, as the consumer rep, if we don't have to go that way, I would be

much happier.

DR. GIBOFSKY: Dr. Bathon.

DR. BATHON: I prefer placebo-controlled trials. We don't have control over when the patient presents, so we can't be responsible for that, but I think it is just really a practicality measure. If they are presenting for treatment, and it's an acutely severely painful condition like this, it is very difficult to enroll people in placebo-controlled trial.

I think we could try it, but I bet you it would introduce yet another layer of recruitment difficulty, so it may make it impractical. I think that until we know data about damage, we can feel reasonably ethically comfortable still that a placebo-controlled trial is fairly ethical in terms of lack of data on joint damage.

If we find down the road by MRI or something that each single attack adds more and more damage to the joint, then, we would have to rethink that.

DR. GIBOFSKY: Dr. Cronstein.

DR. CRONSTEIN: I realize that there is a suspicion based on the RA trials, but the RA trials, you are talking about months of inflammation as opposed to here you are talking about a difference of 12 to 24 or 48 hours. I really don't think there is any reason to think that delaying treatment is going to give you a chronic or more of a chronic problem as far as arthritis goes. I don't think there is any evidence for that.

I think, in fact, there are many patients who have one or two acute attacks over long periods, not sufficient to require a prophylaxis, and they don't have any specific joint injury. I don't think that the worry about that is the main issue.

I just find that if you have something--I know we haven't done the placebo trials--but if you have something that you know works at least as a pain reliever, that depriving a patient with gout, with an acute gouty attack, you know, depriving them of any pain relief, I don't think that is

feasible, and I don't think that we are going to see the same placebo responses that we would otherwise have seen, but obviously we can't do that.

DR. GIBOFSKY: Dr. Boulware.

DR, BOULWARE: I think the placebo-controlled observation for 8 hours would be ideal, too, but I think another layer of practicality is when you enter them, you have 8 hours to do the follow-up study, and unless there is something that the patient is going to do, which then becomes maybe unreliable, it is very impractical to ask my staff to stick around until midnight when you enter somebody at 4 o'clock in the afternoon.

DR. GIBOFSKY: Dr. Geis.

DR. GEIS: Until I saw placebo data for the first few hours after the first dose, I don't know that I would conclude that you are seeing a real effect of a drug or just a placebo effect. It is after seeing just lots of data in different conditions.

You could build in a substudy where you maybe have 50 patients per group where you are looking for this short-term response comparing placebo to the active, so you don't have to build it in for all 150 patients, that you might need to look for the total response over several days, so that may be one way of doing it, and then have specific sites who feel they have the staff to follow up in the first 8 hours, and all of that, so there may be a way you could work it and get both things.

DR. GIBOFSKY: Any further comment on Roman Numeral V? Dr. Schiffenbauer.

DR. SCHIFFENBAUER: The second part of that was the non-inferiority margin and the effect size of any comparator. Did anybody have any other comments about that because that was left unresolved.

DR. GIBOFSKY: I think the question as posed is part of your data from studies of existing therapies. I believe we heard that the data from existing therapies are meager at best, and that

resulted in the design trial that we heard earlier today, which is probably as good as it gets based on the data that is available.

Unless anyone has knowledge of a different data set, but I suspect if there were, it would have been factored by the consultants into the trial design that we heard today.

Let's move to Roman VI. Please discuss the following clinical trial issues: the use of concomitant medications such as diuretics or low dose aspirin. The entry inclusion criteria for an acute gout trial, particularly the need for documentation of the presence of crystals, and to make it perhaps a bit simpler, let's talk about the first attack of acute gout in a person's life versus an attack of acute gout in a patient who is known to have the diagnosis of gout, and then enrollment of patients with polyarticular gout.

Should the trial be stratified by this factor, are there other factors to consider for stratification.

Who would like to begin the discussion on

that? Dr. Cush.

DR. CUSH: I think we already covered the con meds issue of colchicine and allopurinol as background therapy. I think diuretics, I think they are real world, they should be allowed. Aspirin, I think is a confounder as is nonsteroidals, and if at all possible, those patients should be excluded or the low dose aspirin be stopped for the period of study. I am not sure that there is a significant acute risk to stopping 81 mg of prednisone a day.

I think that the entry criteria, I would still advocate the use of the ACR criteria because they are the best studied although I do think that more liberalized criteria should be established because that may be one of the factors that hampers enrollment, and I don't think that crystal identification has to be a part of the mix.

Obviously, it is factored into the equation the ARA used in its deliberations to arrive at criteria, but they are helpful, but not required.

In clinical practice, we all do this, we don't absolutely have to have crystals, we would like to see crystals, but we don't have to have crystals to have a certain or incompetent diagnosis of gout and to proceed with therapy, whether it be acute therapy or more chronic hyperuricemic therapy.

I would argue against polyarticular gout. I think especially if it's first time attacks, Dr. Gibofsky asked do we want to just only go after nascent, brand-new onset gout, but I think that is too restrictive, and those patients are going to be even harder to find, and will require more of a public health kind of campaign for advertising to find those patients.

They are out there, and there is a certain steady flow of them. We have well-defined incident rates, but it will be harder to do. Especially in that population, I would avoid polyarticular gout. In more established populations, I think to include them might be reasonable, but to get to an assessment issue, as Dr. Bathon was talking about,

is which joint do you go after, which becomes your index joint.

Maybe the one you chose as your index joint is really not your worst one, and will not respond as maybe other joint will respond, and there is always the worry of background therapy. Stratification is only going to be I think necessary if you have again a more rapid and liberalized inclusion criteria that allow patients to be seen, consented, screened by clinical parameters, and then enrolled rapidly.

Then you have to basically do a post hoc stratification for things that you might accept not unknowingly, which might include uncontrolled hypertension, renal disease, et cetera.

DR. GIBOFSKY: Dr. Cush, I think you may have misunderstood my comments about crystal analysis. I was referring to bullet 2, where the question would be if you had a patient who is presenting with gout de novo and no history of gout, would you prefer the crystal analysis to the six Wallace criteria as opposed to a patient who is

known to have a diagnosis of gout, would not the Wallace criteria suffice, in which case you would not need the crystal analysis.

In other words, the first patient comes to you in clinic with what looks like podagra despite the discomfort of the arthrocentesis, wouldn't you want to know that you are dealing with monosodium urate as opposed to your patient who has been with you for five years, who comes in and says here I am again.

DR. CUSH: And I believe that the actual paper, the Wallace criteria paper from 1977 deals with this fact and comfortably allows you to make the diagnosis in either situation, with or without crystals. It is very clear by the inclusion of crystal identification, you increase the specificity of diagnosis to 100 percent. That is absolutely true. But without it, you don't lose that much, you are down 10, 15 percent I think at the most was the number that was in the paper.

So, just by going like clinical criteria alone, if you make it, then, you are going to be

in. Of course, it is always great to have crystals, but I don't think you need to do it from the standpoint of having diagnostic criteria. I think the diagnostic criteria were developed to allow for that degree of leeway, but then again, this is really a point most pertinent to going after patients for first time attacks.

If that is the sole kind of study one wants to do, you are going to have trouble, and it is not the trouble in identifying crystals and making the diagnosis, it is trouble in finding the patients.

DR. GIBOFSKY: Dr. Williams.

DR. WILLIAMS: I would argue that I would like to see the diagnosis by the demonstration of crystals at some point. There are so many patients out there who say they have gout, who we can't document they really have gout, that at some point in the course, I would like to have crystals demonstrated. After that, I am perfectly willing to rely on the criteria that say that that current attack is an attack of gout.

DR. GIBOFSKY: Dr. Cronstein.

DR. CRONSTEIN: I think as Dr. Cush pointed out, somebody who comes in with an acute podagra, it is pretty unlikely it is going to be anything else. The discomfort of the tap, you know, adds to the difficulty in recruitment if that is going to be an issue, and then finally, a lot of emergency rooms are probably not going to be equipped for appropriate crystal examination.

So, I think that even though it is a small percentage of the patients, you said it was 10 or 20 percent, something like that, a small percentage of the patients, I think that might hinder recruitment, and I don't think that we necessarily need that level of documentation.

DR. GIBOFSKY: Dr. Schiffenbauer.

DR. SCHIFFENBAUER: Would there be any concern if there was an imbalance in the groups, the treatment groups, for those that had crystal identification versus those that don't because of the false positive or false negative rate, that issue, do you either require that everybody have it

or everybody use clinical criteria just to avoid that possibility?

DR. GIBOFSKY: Dr. Hochberg.

DR. HOCHBERG: I would actually be consistent with the way in which other rheumatic conditions--I hate the word rheumatic--other arthritis conditions are described in draft guidance documents and in entry criteria, that the patient has a clinical diagnosis of and fulfills American College of Rheumatology classification criteria for is often the way that studies are recruited for, that protocols are written, protocols are agreed upon by the sponsor and the Agency, and papers are written.

That is how we do it for rheumatoid arthritis and oftentimes for osteoarthritis, not all the time for osteoarthritis, so I think somebody with a clinical diagnosis of gout, who fulfills what granted are old, but haven't been revisited criteria for gout would buy somebody into a study.

Some of those people will be aspirated for

crystal identification, and that is how they will fulfill them, some of them won't, and I think that ought be reported in a paper, and that could be compared as part of the table 1 baseline data in a paper and clearly be reported in the report that comes to the Agency for the Agency's review, and if the Agency notes an imbalance, the statisticians can look at it and decide how they want to deal with it.

I would stratify on polyarticular gout if I was designing a protocol, because I think, you know, there is a suggestion that the time to response may be different because of the burden of disease and the number of joints involved.

DR. GIBOFSKY: Dr. Bathon.

DR. BATHON: I agree strongly with what Dr. Cronstein said earlier about not requiring an arthrocentesis, but the only thing I am concerned about is that if this trial were done heavily in primary care practices or emergency rooms, I think a lot of rheumatologists amongst us are skeptical about the validity of joint exams done by

non-orthopedists and non-rheumatologists.

Many patients come to us with supposed joint swelling and joint findings that we can't corroborate, so that would be an issue, you are just relying on clinical criteria.

DR. GIBOFSKY: What about Dr. Schiffenbauer's question, should whatever criteria that are adopted be uniformly applied, requiring either crystals for all or crystals for none?

Dr. Williams.

DR. WILLIAMS: I agree with Marc. I think that if you are going to accept the criteria, the 12 criteria, you allow them to have either way to make the diagnosis, those are the guidelines.

DR. GIBOFSKY: Further comments on any of the bullets listed here? Is the Committee comfortable with the recommendations about stratification, inclusion criteria, and the use of concomitant medications?

Dr. Hochberg.

DR. HOCHBERG: I would like to ask a question about concomitant medications. Are there

any data on whether low-dose aspirin, 81 mg, has an analgesic effect?

DR. GIBOFSKY: Any data from the Agency perhaps?

Dr. Cronstein.

DR. CRONSTEIN: I am not aware.

DR. GIBOFSKY: Well, you were sitting next to Dr. Schiffenbauer. Guilt by association, Dr. Cronstein.

DR. CRONSTEIN: I am not aware of any data.

DR. HOCHBERG: There was a prior comment made to discontinuing low-dose aspirin on entry into a trial, and if there is not an analgesic effect of low-dose aspirin, then, why would it be discontinued in somebody who might be on it especially, you know, somebody at risk for coronary disease or has had a prior thrombotic event and has gout, and comes into a trial. I mean I would probably want to leave them on it.

DR. GIBOFSKY: I think that is a fair question.

Dr. Williams.

DR. WILLIAMS: Actually, Jack was the one that made that point and he has gone, but the reason would be is because of its effect on uric acid retention in low doses. I think that you could make the case for just continuing their medications at the same stable dose and make just as much sense.

DR. GIBOFSKY: Dr. Cronstein.

DR. CRONSTEIN: I think the same could be said for diuretics, and there you can lose control of hypertension if you stop them, so I think that things should just continue.

DR. GIBOFSKY: I think we would be comfortable with continuing concomitant medications at the stable dose that the patient is on at the entry of the study. I believe we have discussed bullet 2.

Any further comment on stratification by other factors? I think we have talked about polyarticular gout. Anyone want to make any other comments about stratification?

DR. HOCHBERG: Could I ask you a question?

DR. GIBOFSKY: Please.

DR. HOCHBERG: Do we know whether there are any other variables that affect the response to treatment in patients with acute gout, that we might want to stratify on because they might be associated with response?

DR. GIBOFSKY: I am sorry Dr. Terkeltaub isn't here and Dr. Cush has gone. Dr. Cronstein.

DR. CRONSTEIN: The question is whether you have somebody who has an acute attack on top of chronic tophaceous gout and whether they ever get back to baseline, and I think that that is problematic.

Were there many patients in your trial that had chronic tophaceous gout or did you exclude them?

DR. MELIAN: I don't have the exact number, but I think we had about 10 to 20 percent of patients that fell in that general category. I don't have the numbers in front of me, so I am stretching here a little bit, but I think it was in

that general ballpark.

DR. CRONSTEIN: Do you know if there was a difference in response, because if they already have structural damage to the joint, is that going to interfere with your ability to--

DR. MELIAN: That is something that we would have to go back and look at the database. We think if anything is going to have an impact on the things that we have looked at, it would be baseline pain where patients with more severe pain tend to have a greater improvement.

DR. GIBOFSKY: Dr. Williams.

DR. WILLIAMS: We did not address allopurinol and I assume the patients who were on chronic allopurinol would remain on like we do with diuretics and aspirin.

There is some, I don't know if it's evidence based, that starting allopurinol can prolong the attacks of gout, and if they got put on allopurinol, I assume they would have been put on other medications and not qualify for the trial anyway, but if someone were just put on allopurinol

acutely, or if that should be stopped or at least stratified.

DR. GIBOFSKY: Dr. Bathon.

DR. BATHON: Apparently, some complementary and alternative things that are out on the market have steroids in them, so we might just say restrict those kinds of things.

DR. GIBOFSKY: Any further comments about Roman Numeral VI? Any further comments about any of the issues we have been discussing this afternoon in response to the questions posed to us for consideration?

Any other questions from you, Dr. Schiffenbauer, for our consideration? Anyone?

If there are no further questions from the panel or issues to discuss, Dr. Harvey, would you like to make some concluding remarks?

DR. HARVEY: First of all, I would like to thank you all for your service to the Committee. I really believe that these last two days have been very productive and have had a lot of good discussion on all the different areas that were

outlined in the agenda.

I really think that this discussion and what we have done yesterday and today will lead to future clinical trials for new therapies for patients who are currently suffering, so I thank you for your service.

DR. GIBOFSKY: Thank you. I would like to thank the members of the panel for their spirited and considered deliberations these last two days. I would like to thank you once again for making my job so easy and hopefully, yours so enjoyable.

I will declare this meeting adjourned.

[Whereupon, at 2:08 p.m., the meeting adjourned.]

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