FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE

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The Ballrooms
Holiday Inn Gaithersburg
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Gaithersburg, Maryland

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C O N T E N T S

C O N T E N T S

P R O C E E D I N G S (8:10 a.m.)

DR. ABRAMSON: Good morning, everyone. Can everyone please take their seats, so we can begin?

I'd like to welcome everyone. I'm Steve Abramson from NYU and the Hospital for Joint Diseases. I think we have a very interesting day ahead of us, discussing very important issues regarding osteoarthritis, and a lot of expertise, both on the panel and in the audience. So we look forward to a very excellent and lively discussion.

I'd like to begin the meeting by going around and asking the committee and the guest consultants to introduce themselves, please.

DR. DOUGADOS: Should I start?

DR. ABRAMSON: Yes, Maxime.

DR. DOUGADOS: Yes. Maxime Dougados. I'm a rheumatologist working in the Department of Rheumatology in Paris, France, and my clinical research is focused on clinical epidemiology and overall in osteoarthritis outcome measures and x-ray evaluation.

DR. PUCINO: Frank Pucino, Pharmacy Department at the NIH.

DR. DIEPPE: Paul Dieppe. I'm a rheumatologist in the U.K., based in Bristol, special interest in osteoarthritis. I also now run the Medical Research

Council's Health Services Research Collaboration in the U.K.

DR. ANDERSON: Jennifer Anderson. I'm a statistician in Boston University, and I'm not working currently in arthritis, but did for a dozen years.

DR. HOCHBERG: Marc Hochberg. I'm a rheumatologist and head of the Division of Rheumatology at the University of Maryland School of Medicine in Baltimore. Also trained as an epidemiologist and have a secondary appointment in the Department of Epidemiology and Preventive Medicine.

My research is in epidemiology of osteoarthritis as well as in clinical trials, and I co-chaired with Roy Altman the effort by the Osteoarthritis Research Society to develop guidelines for the conduct of clinical trials in osteoarthritis.

DR. YOCUM: Dave Yocum, University of Arizona. I'm a rheumatologist and part of the Arthritis Advisory Committee.

DR. BRANDT: Ken Brandt, Indiana University. I'm a rheumatologist, a member of the committee, and have broad interests in osteoarthritis, basic clinical and health services research.

DR. SHERRER: Hi. I'm Yvonne Sherrer from Fort Lauderdale, Florida. I'm a rheumatologist, and I'm on the

advisory committee.

DR. HARRIS: I'm Nigel Harris. I'm a rheumatologist and member of the Arthritis Advisory Committee. I'm currently Dean of Morehouse School of Medicine.

DR. MORELAND: I'm Larry Moreland, a rheumatologist at the University of Alabama at Birmingham and involved with clinical research in musculoskeletal diseases.

MS. MALONE: Leona Malone, the consumer representative.

DR. LOVELL: Dan Lovell, pediatric rheumatologist, University of Cincinnati.

DR. ELASHOFF: Janet Elashoff, biostatistics, Cedar-Sinai and UCLA.

DR. WITTER: Jim Witter, Medical Officer.

DR. JOHNSON: Kent Johnson, Medical Officer.

DR. HYDE: John Hyde, Acting Deputy, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products.

DR. MIDTHUN: Karen Midthun, Acting Division Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products.

DR. ABRAMSON: Thank you.

I'd like now to introduce Kathleen Reedy,

Executive Secretary of the committee, to read the meeting statement.

MS. REEDY: The following announcement addresses the conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

In accordance with 18 United States Code 208, General Matters, limited waivers have been granted to all committee participants who have interest in companies or organizations which could be affected by the committee's discussion of the evidence needed to establish that a drug product has a beneficial effect on joint osteoarthritis.

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, Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda, for which an FDA participant has 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 involvements with any firm whose

product they may wish to comment upon.

DR. ABRAMSON: Thank you.

I'd like to introduce Dr. Midthun to address the audience.

DR. MIDTHUN: Good morning, and welcome to today's meeting of the Arthritis Advisory Committee.

FDA is currently in the process of drafting a guidance document that addresses clinical development programs for drugs, biological products and devices, intended for treatment of osteoarthritis, and thus we especially look forward to today's input and discussion regarding study endpoints, including structural endpoints, and other important issues that might be considered in the clinical conduct of osteoarthritis trials.

Thank you, and I would like to now introduce Dr. James Witter, Medical Officer, the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, to lead off the discussion.

DR. WITTER: Good morning. There's going to be a little change today. I was scheduled for about a 10-minute presentation. I've changed it a little bit with the blessings of everyone involved, I think, that my talk will be more in line with something called "Safety Endpoints and Surrogates," and it might take a little bit longer, but I hope we have enough time today to discuss everything

adequately

This talk is really intended to raise issues and not kind of solve things. I'm just trying to create some context here that we might discuss things later. So the title of this is "Structure Modification: Is it Worth the Risk?"

Next slide.

Can we in fact all agree that osteoarthritis is really the following? It's the most common form of arthritis. It is painful. The pain ranges from intermittent to disabling that in fact requires surgery, and that there is currently no therapy that alters this natural history. This is in spite of claims in the popular press for certain compounds that would allude to that.

Next slide.

The concept as the joint as an organ has evolved, which I think is a very useful concept. In particular, the joint has several components to it, as most of us well know, including the cartilage, the menisci, tendons, the bone and the periosteum, the synovial fluid in the membrane and muscles.

One thing that strikes me as very interesting is looking at particular the idea that the cartilage is neural which certainly would seem to speak to the fact that whatever is going on in the cartilage would not be

reflected by any measure of pain, and so if there's a disassociation between pain and what happens in the cartilage, it might not be surprising.

Next slide.

Now, this is actually the second meeting to discuss the guidance document and the contents thereof, and I'd like to just use a few seconds here to set a context.

We do have in fact an existing or extant guidance document. It was written in 1988, and it really describes treatments that were consisting of primarily drugs and devices, but no biologics. These were either DESI'd in or by NDA review, and in that 1988 guidance document, the labeling reads "is indicated for acute and long-term use in management of signs and symptoms of osteoarthritis," and in that document, there were no primary endpoints that were really laid out, which I think is really different in substantial ways than the document that you have today.

Next slide.

I'd just like to take a few minutes and describe the process, some of you are familiar with this, some of you are not, as to how these documents actually kind of evolved. It is certainly an interesting process, and I kind of liken it to, in my little picture here, trying to illustrate that there are many different thought

processes, which hopefully we'll get some more today, and somehow this goes through a process which then comes out with a guidance document.

But to kind of just lay it out, we have certain therapies that go to, let's say, certain aspects of the disease in OA, that go to either us in Drugs, to our colleagues in Biologics, and I'm happy to see that Dr. Schwieterman is here, and Devices, and we then meet on a regular basis as a rheumatology working group. We try and develop from this aggregate experience a consensus and come up with a consistent approach and then try and explain this and put this down in a document which you have before you today.

Now, this is an iterative process internally, and part of today's intention, I think, is that it's also iterative with the outside as well. We're looking for input.

Next.

Now, in the document is discussion, kind of the connection between pain and structure, and we all have been wrestling with that, and some of the thought processes that have gone into that discussion, at least internally, is the question as to whether for a treatment that will regard structural damage, must it also improve pain, and in fact, is structure a superior reflector or predictor of important

outcomes compared to traditional symptom measures, and these are some of the issues that we wrestle with.

Next.

In terms of structural changes in OA, the question has been kicked around as to whether does joint-space narrowing currently an accepted marker for hip or knee OA really adequately reflect what structure means? That kind of alludes back to the idea of the joint as an organ, and maybe we're not looking at the right kind of structural target.

What is then the change in the joint-space narrowing of the hip or knee that is clinically relevant, which I think is a very important topic that we'll hopefully get a handle on today. What does that mean to everyone or what should it mean?

And the hope that ongoing research in MRI and cartilage markers, bone density, and arthroscopy, for example, there's certainly a big hope that this will facilitate future development.

Next slide.

We can't talk about these endpoints really without kind of bringing up the concept of surrogates. I'd like to just discuss that for a second. Generally, it's agreed that total joint replacement represents a failure of this organ then called the joint. The current "surrogates"

in OA include things like biochemical and molecular markers, MRI, and does that in fact really include x-ray and joint-space narrowing, and it's really unclear how structural damage correlates with pain and disability, but I think it's fair to say that all are necessary for total joint replacement. Normal joints do not get replaced, for example. It's only when there's sufficient structural damage and sufficient pain and disability that the joint is eventually replaced.

Next.

So what is a surrogate endpoint from the perspective of the agency? It's a laboratory measurement or physical sign used as a substitute for clinically-meaningful endpoint that measures directly how a patient feels, functions or survives.

The treatment effect on the surrogate should reflect treatment effect on clinical outcome, and should be in fact prognostic for the clinical outcome.

Next slide.

Now, how are surrogates used in aggregate in the agency, for example, and also this would be on the outside. During Phase I/Phase II, for example, to help us identify promising new agents. During Phase II, to help prioritize those promising agents for further study. During Phase III, to help assess efficacy, and during Phase

III/IV, to help compare active and effective treatments.

Next slide.

But there are some problems with surrogates, some that are well known to some of us. One of the problems is that surrogates do not always account for adverse effect, which may cancel out part or all of the apparent treatment benefit, and I think probably the best example is the cardiac arrythmia suppression trial or the acronym CAST published in the New England Journal in 1989, which is in essence the realization that post-MI arrhythmias treated with what were then very effective anti-arrhythmics were associated with worse survival. In fact, they were going the wrong way.

Next slide.

There are other problems. Sometimes surrogates do not always account for beneficial effects which may occur via a pathway that does not include the surrogate, and an example here, for example, is use of Interferon in chronic granulomatous disease published in the New England Journal in '91.

Here, the trial demonstrated that there was in fact a major reduction in serious infection, but it was without effect on the proposed surrogates which were superoxide production and bacterial killing.

Next slide.

So it raises the general question as to, to what extent can a surrogate which is validated for one product be considered reliable for another product? For example, there may be different causal pathways for efficacy, and there may be different toxic effects.

Next slide.

The way that this has been handled is by something called accelerated approval which I've given you the citation here, if you care to look it up, if you don't already know it, but in essence, it reads, "The FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on the surrogate endpoint that is reasonably likely based on epidemiologic, therapeutic, pathophysiologic or other evidence to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible mortality."

Next.

Now, the accelerated approval was first proposed in 1991. It was finalized in 1992. It is intended to be limited to serious and life-threatening diseases. It is supposed to be for therapies that have the potential for advantage over existing therapeutic options.

There's a requirement in fact that the studies

to evaluate the clinical effect of treatment be ongoing, and that drugs ultimately -- and when I say drugs, I mean biologics and devices; drugs is just a handy term for us here -- that drugs ultimately found to have no clinical effect could be withdrawn.

Next slide.

So with that said, I'd like to switch a little bit to just some considerations of safety because the issue of surrogacy and the issue of accelerated approval and kind of trying to get the concept out of clinical benefit, certainly we get into what are some of the safety issues involved, and I thought I'd use something that might serve as a useful example here.

Some of the pluses and minuses may not exactly correlate here. I'm just trying to get out concepts. This should not be construed as anything in terms of our part that we're saying one thing or another about anything that I'm showing up here. It's just to kind of get out some of the concepts.

So for example, as we might think about a very rigorous endpoint of death, and looking at two agents, NSAIDs and COX-2 agents, we certainly are all aware that NSAIDs are associated with deaths. If you believe the ARAMUS database, for example, there's in excess of 16,000 deaths conservatively with NSAIDs, and there are, as we

also know, some deaths associated with liver problems.

Now, in terms of the COX-2 agents, the hope is certainly that this will be improved. So we've kind of gone from, let's say, three to two or one, however that may ultimately pan out, but hopefully they'll turn out to be safer, and in fact, we still may have the same number of liver deaths, but as you kind of total this up, overall, the pattern, the safety pattern in terms of looking at this endpoint for COX-2 agents may in fact be better than for NSAIDs.

Next slide.

But what happens if something happens in the safety profile that was really not expected? How does that change our thinking about the relative safety? So for example, here, I'm just looking at the same endpoints, but I've added in cardiovascular events, and let's just say that there are none that are associated with NSAIDs, but there are some associated with COX-2 agents for whatever reason, and although they may be small, they certainly are something that is worrisome.

How does that then factor into this equation? Does this change it substantially or does it change it not much at all? You know, that's something that maybe we could discuss today, but it's the basic concept.

Next.

So taking this and then looking at the safety profile of some of the therapies that are currently employed in OA, it might then be useful for us to look at how the overall safety's evaluated, looking, for example, at adverse events, serious adverse events, and deaths, and I think it's safe to say that for NSAIDs, we are certainly all aware that all three of these problems exist with NSAIDs.

With APAP or Tylenol, it's not as well recognized, but it certainly is the case that there are adverse events, serious adverse events, and deaths associated with the use of Tylenol. It's not an innocuous compound.

I've put up here the visco supplements as they currently exist, and I was hoping that Sahar would be here today, but let's just for the sake of argument, let's assume that no therapy is without an adverse event. I do believe that there are some serious adverse events associated with the disease. I do not think at present there are any documented deaths associated with this therapy. So let's just say for the sake of discussion, it kind of comes out like this.

Comparing that then against other therapies for OA in terms of end-stage disease, looking at here total knee replacement, you could put in there total hip

replacement, basically the concept of surgery, and again I think we're all aware that there can be adverse events, some of which can be serious, and certainly there are deaths associated with this as a treatment modality. So it's not an innocuous therapeutic option.

And then comparing against weight loss, which is certainly one way that's been recommended to improve symptoms, and I would venture to say that some people would argue that hunger pains are adverse events. So we get something there.

In terms of serious adverse events or deaths, let's just say for the sake of this discussion that there's nothing to be concerned about.

Next.

Now, how would this safety profile compare then putting in just for the sake of today's discussion MMPs, and we won't define that as to what they are, examples of it, where they are. It's just the idea that there is something called MMPs that is going after structure modification in OA, and how might that stack up?

Well, we'll use the same rule that there are always adverse events with any therapy, and at the present time, it's unknown whether there are any serious adverse events or deaths associated with this modality, but it may be that, for example, they may look more like the visco

supplements than they'll look like NSAIDs. So that kind of factors into our equation.

Next.

Well, what then could we maybe hope to get out of a structure modification-type compound? In this cartoon, what I've tried to do is maybe hopefully depict something here that is useful. Using the dotted line as our endpoint, be it pain, overall pain, pain on a day, whatever kind of pain you're interested in, and here joint replacement, and that for any particular individual kind of varies up and down, and here would represent the particular trajectory that a person has in terms of their time to when they develop pain or when they would develop replacement, and that with each individual would go up and down and vary. The slope varies without therapy.

With therapy, I think the hope is with something that would slow or arrest joint damage is that this would shift, and the time to developing serious pain or coming to a joint replacement would in fact be shifted to the right. If that were true, then what we might be doing is changing the overall safety profile because we're getting rid of some of these potential confounding therapies.

Next slide.

So what might we get? In terms of the efficacy

then, without structural therapies, as we currently have it today, I think it's safe to say that we certainly modify symptoms, but we don't modify structure, and we're not aware that we're modifying any functional outcomes.

What might the efficacy with structural therapies look like in the future? It's safe to say then again that we're modifying symptoms. One would hope that we certainly would be able to say that we've modified structure because that was the endpoint, and still in terms of functional outcomes, we have to leave it as a question mark.

Next slide.

And then what do we get for that then in terms of the overall safety profile for that, what is hopefully, added benefit of efficacy? Well, one could maybe argue that the present safety profile, we have the COX-2 agents or the NSAIDs and COX-2 agents contributing a certain amount of risk, and surgery contributing a certain amount of risk, and in the future, if it turns out to be true, for example, that COX-2 agents have a better safety profile -- I've switched it around here, and you see I've changed the font. So maybe in fact the risk might be slightly lower with the MMP inhibitors or those kinds of therapies. There might be some risk but maybe not a lot.

What would we do, for example, if these new

modalities had some other benefit on clinical outcomes, reversing the question before of cardiovascular events and being potentially increased by COX-2 agents? What if in fact those kind of events were decreased by these kind of agents, how would that factor in, and then surgery would hopefully be playing a lesser role, so that the overall profile in the future with these types of compounds may look quite different.

Next slide.

And then just a general question and something maybe to think about in terms of an adverse event, of something like, for example, shoulder fibrosis. How should we be viewing that? Is that really a safety issue in the sense that we should be discontinuing that dose all together and not really study that dose anymore or should we really view that as an efficacy issue in the sense that we should just be lowering the daily dose or taking drug holidays and using intermittent therapies? How should something like that be viewed?

Next slide.

So in terms of today's discussion then, in terms of OA and clinical benefits with structure-modifying compounds, what do we mean when we say something is worsened? What do we mean when something is improved? What do we mean when something stays the same?

Next slide.

And so in terms of structure, OA structure, what should our motto be? No pain, no gain? In other words, if you don't have an impact on pain, you don't get it on the market or something like that or an ounce of prevention is, and you can fill in the rest.

Thank you.

DR. ABRAMSON: Thank you, Dr. Witter.

Are there questions for Jim?

(No response.)

DR. ABRAMSON: I'm just curious. In the experience with the accelerated approval process that you described, what kind of postmarketing surveillance has there been, and have you had occasion to actually reverse the decision where surrogate markers in fact turned out not to be validated?

DR. WITTER: I'm aware -- and Bill or Jeff, you can correct me -- that compounds have been removed from the market. The exact processes in terms of how that came about, I don't know all the details, but there have been compounds that have been removed.

DR. ABRAMSON: All right. Thank you.

We'll next ask Dr. Brandt to give a discussion on a design model.

DR. BRANDT: The title, I think, is perhaps a

little bit obtuse. I think I've been asked to speak for a couple of minutes because in essence, I'm a guy on the firing line who's in the midst, up to his elbows, you might say, in doing a clinical trial of a potential disease-modifying OA drug, and I want to comment in a couple of minutes rather specifically on what we're doing in that particular narrow context.

Could we have the first slide? Oh, it's there.

Just to sharpen the perspective, what we really want to do, what Jim has been talking about, is the development of a structure-modifying drug, something that can be administered to a patient.

I don't know if there's a pointer here or not. Yes, there is a pointer here. Thanks very much.

That can be administered to a patient, for example, with relatively mild structural changes with pretty fair preservation of joint-space width but not normal, subchondral sclerosis, and if we have the lights down, we'd see a definite osteophyte there, and the potential to do something pharmacologically or with a biologic agent that prevents or slows the progression to something like that over the next, you pick it, three years, five years or so, with the assumption that this is going to do something good symptomatically, and we have no clue whether it will do anything good symptomatically or

not.

This is a relatively new interest in both academia and in the industry, and there are reasons why we've been slow to leap on this. One is the presumption that the rate of progression of the disease is slow, and if we look at incidence figures or progression figures, they're something like this. Most people don't show much change very quickly, at least by the outcome measures that we currently apply, and the biomarkers, surrogate markers that Jim has touched on, in 1999 still leave a good deal to be desired.

One of the things that in my view has impacted on that and changed things to a considerable degree has been evidence from epidemiologic studies that there may be joints that are particularly at high risk for developing OA or progressing with the disease more rapidly than others, and the standardization of this outcome measure, knee radiography, and we'll talk more about that today.

But for example, from work by Tim Spector in the U.K., for example, a subset has been defined of women of a certain age who are obese in the upper tertile of the population for body mass index, who have radiographic changes on a plain x-ray in one knee but not in the other knee, and this is a high-risk population from the standpoint of OA because according to Tim Spector's data,

the risk of acquiring incident OA based on plain radiograph in that contralateral knee that was normal at the outset is 50 percent within two years, and that's sufficiently high enough figure to make that of considerable interest for people who are trying to develop drugs. We might get an answer in our lifetime.

Standardization of knee radiography is the other important issue, and there are a number of people, including Maxime Dougados and others, who have given serious thought to this, for protocols for standardizing knee radiograph, and we've listed some of them here, and I would point out that all of these use fluoroscopy, fluoroscopic positioning, to achieve the radio-anatomic alignment of the beam with the medial tibial plateau, and that's a limitation.

It's logically difficult. It's an inconvenience. It works to a degree, but it's not so simple. So there are efforts underway to do this, to achieve the same thing essentially with non-fluoroscopic positioning methods, and those are things that are in progress, and we look at those developments there with considerable interest.

I'm sorry. Going the wrong way. The experience in our clinical trial is with the Buckland-Wright technique, using fluoroscopy, and these are the

criteria for satisfactory positioning. A magnification marker is placed over the head of the fibula, rotation of the knee is controlled so that the tibial spines are centered within the femoral notch, and flexion of the knee varies from from knee to knee, but is achieved so that the anterior and posterior lips of the medial tibial plateau are superimposed radiographically.

We've looked at the exportability of that technique in clinical centers and looked at five independent x-ray centers in Indianapolis and sent 42 patients with knee osteoarthritis to be radiographed twice in one center and twice in another of those five centers, so that we have four images obtained within a week or two on 42 patients, and we looked at how satisfactory from a technical standpoint things were with -- when both images were satisfactory, the standard error of the mean for medial joint-space width was very good. When neither image was satisfactory, things were not nearly so good, and when the technicians did things right, and this was after a period of instruction and bringing them into practice and giving them a manual and sending some practice patients before we actually undertook the study, I can't tell you it ain't simple.

When they do it right, the technique is good. It performs as well as essentially as was described by the

author of the technique, Chris Buckland-Wright, but the problem is a human problem in getting technicians to do things right, even with those efforts.

Why do we care about that? Why is standardization important? Well, the precise numbers here aren't so important, but as the precision of measurement becomes better and better, we need fewer patients, fewer knees per group to determine a significant drug effect, or we could flip the numbers around and say with a finite number of patients, we can get a result in a shorter period of time, and both of those are advantageous to people who are trying to develop a drug.

Let me say now just a couple of things specifically about the clinical trial that we're doing, and this is a study of doxycycline, a placebo-controlled randomized trial involving six centers. The basis for this came out of an interest in our lab a few years ago in minor collagens of articular cartilage and particularly type 11 collagen. About 1 percent of the collagens in articular cartilage, 1 alpha, 2 alpha, 3 alpha. It's a helical molecule. Here are the three chains, and in osteoarthritis, whether it's canine or human osteoarthritis, there is a fragmentation and lower molecular weight products of type 11 collagen, and the basic question that we asked was how does that happen?

Interstitial collagenase didn't degrade this molecule. Nothing known to man at the time we undertook those studies degraded this molecule, and that was the basic interest, and it turned out that this was degraded by a 72-kilodalton gelatinase which has now been well characterized as a typical matrix metal of proteinase, and I won't go into the chemistry, but those results of characterization of this as a metal proteinase led us to toss some doxycycline into the test tube as this gelatinase was degrading type 11nase, and we found that in vitro, we were able to inhibit very effectively that enzymatic activity with reasonable concentrations of doxycycline, and that led then to this in vivo study in an accelerated canine model of osteoarthritis of ours, and here we see without treatment, eight weeks after we cut the cruciate ligament in the knee of a dog which previously has undergone extensive interruption of sensory input from the ipsilateral hind limb, we have severe extensive osteoarthritis on the femoral condyles, and this tan material is the underlying subchondral bone with full thickness loss of cartilage occurring very, very rapidly in this model, and we were able to achieve that with three and a half milligrams per kilogram.

That has been confirmed in other labs. The effect can be seen when the drug is administered

therapeutically rather than prophylactically. Chemically-modified tetracyclines have had effect in other models, and this has led to the NIH-supported clinical trial that I've mentioned.

We're using specifically patients with the high-risk knee characteristics that I described. That limits the generalizability, but it was an expedient, we felt, and with an NIH budget rather than a plush industry budget, we felt rather constrained in that regard, and we recognized that this may indeed limit the interpretation with regard to generalizability.

Six clinical centers. Here are the number of subjects. We have randomization as well advanced there, about a hundred subjects yet to be recruited. I hope we're done with that phase by the end of this calendar year. The dosing on a mg per kg basis is equivalent to what we had in the dog, and this is sufficient to inhibit both collagenase and gelatinase, active and total enzymes in both cases, and extracts of OA cartilage from humans.

We've applied a faintness of heart test because compliance and subject retention are major concerns. With using the computerized medicine cap, all eligible candidates are given four weeks of placebo pills in the same dosing regimen and required to show up back to the clinic for two appointments and to maintain as defined by

the computerized medicine cap 80 percent therapeutic coverage during that period of time.

All other criteria having been met, if the patient fails this test, they are not randomized to drug, and I think that's helpful. 30 months, fairly substantial period of time, bi-monthly follow-up, primary outcome measures, both joint-space narrowing on digitized films with a computerized measurement of medial compartment, and progression of bony features, such as osteophytes in particular, secondary outcome measures, pain and function, and here's where we are to date.

We effectively started in May of '97. This is where we want to be by New Year's Day, not too bad. We'd like to see no yellow in here, but we're not too bad. As I say, there's about a hundred subjects yet to be recruited. It looks as though our dropout rate is a little lower than what we had anticipated. So we'll see.

This is baseline data of the two treatment groups blinded to us, but from the statistician, Group A and Group B, one is doxy, the other is placebo, matched at baseline with regard to everything actually. BMI, 80 percent or so are white. Index knees, all requiring Grade 2 or Grade 3 Kellgren and Lawrence, similar in the two treatment groups. Contralateral knee's essentially normal, Grade 0 or Grade 1, in the two groups.

Recruitment is a hassle. Patients derived from clinic populations tend not to have too often too much bilateral disease to be eligible for this study based on our criteria. So we go to the community, and potential subjects obtained from motor vehicle licenses and women's health initiative and so on.

One of the consequences of that is that pain is not as severe as you might expect out of a clinic population of patients with osteoarthritis, and here these are WOMAC scores for the index knee and the contralateral knee, and this is relatively low, and it's going to limit our ability, I think, perhaps in the long run over 30 months to assess to what extent the active treatment has an effect on symptoms.

And discontinuation of study drug as the dropouts are lower than we had anticipated by about a third, and most patients are dropping out relatively early on in the study. There's pretty good retention once they get past the first six months, and this is something that -- and the reasons vary. It's moving, it's getting tired of the stringency of the protocol, adverse events, not a terrible problem, nothing serious at all to date that has been considered to be drug-related, some degree of monilial vaginitis, which has led to one discontinuation only, and some non-specific GI complaints, no serious problems, and

one or two dropouts for that particular reason.

So this is something, I think, that we want to work on with the nurse coordinators in particular to see if it is possible to maximize retention and keep the subjects invested in the study, but once we get past this, there are some things -- it still is early days, obviously, but things are going reasonably.

Those are the specifics. That's what we're doing, and I'll breathe a sigh of relief on New Year's Day if we hit our recruitment objective, but I think we should be close, and thereafter, I think we'll have some interesting data.

We will do an interim analysis next, I think, May on the first patients who have had 16-month follow-up x-rays.

Thank you.

DR. ABRAMSON: Kent?

DR. JOHNSON: What percent of the enrolled patients have an asymptomatic contralateral knee?

DR. BRANDT: Most.

DR. JOHNSON: Most of them?

DR. BRANDT: Yes. Even the symptomatic ones, you see those pain scores are really pretty low.

DR. JOHNSON: Did you x-ray the contralateral knee?

DR. BRANDT: Both knees are x-rayed, yes.

DR. JOHNSON: And what what percent of the enrollees have a normal x-ray in the contralateral knee? Most of them?

DR. BRANDT: 100 percent, either Grade 0 or 1, 100 percent by definition.

DR. JOHNSON: What percent have zero grade, have a normal x-ray, do you think? Do you know?

DR. BRANDT: Well, I had that up there. I think it's 60 percent are Grade 0.

DR. JOHNSON: Okay.

DR. BRANDT: But to split hairs between a Grade 0 and a Grade 1 Kellgren and Lawrence, a lot of that is in the eye of the beholder, and the reproducibility of that grading between 0 and 1 is something that I'm not at all confident in as we go back and look at the same films a week apart. This is pretty shaky stuff.

DR. ABRAMSON: Dr. Dieppe?

DR. DIEPPE: Thank you. I wanted to make one comment and ask one question. The comment is that I think the recruitment from the community versus recruitment from clinics may make a very big difference, and it's a crucial issue, I think, in this discussion because most of the data we have has come from populations recruited from clinics, and that may not be generalizable to the community

population. So that's the comment.

The question, which is not unrelated, is about concomitant therapy, and what percentage of patients were taking what sort of therapy prior to the start of the trial, and what are you doing about other therapies through your 30-months duration, because that's a big problem in studies of this sort.

DR. BRANDT: It sure is. We've permitted concomitant therapy. The only thing that we excluded was high-dose aspirin, anti-inflammatory dose aspirin. I don't remember what the cut-off was, but -- and indomethacin. Everything else we're tracking. It's permitted. We've added glucosamine questions once this became an issue after this study began, but we felt that we would have a disaster on our hands if we attempted to eliminate concomitant therapy or mess with it in any appreciable way. Without a study of that duration, I don't think that it's feasible.

DR. ABRAMSON: Other questions from the committee?

(No response.)

DR. ABRAMSON: Okay. Thank you, Kent.

At this point, before we go on, we'd like to open up to the audience, if there are members with expertise, either from academia or industry, that would like the committee during the day to consider questions

other than those that are posed in the protocol that you have before you. This could be an opportunity, if anyone would like to add anything to today's agenda.

DR. ALTMAN: This is Roy Altman from Miami. In the draft document, there's no comments on arthroscopy, and I thought that that should be discussed.

DR. ABRAMSON: Any other suggestions?

DR. SCHWIETERMAN: Dr. Abramson, I'd just like to answer the question that you had raised at the end of Dr. Witter's talk about the number of products that have been withdrawn by the agency after receiving accelerated approval.

To my knowledge, there have been none across the agency, and I'm reasonably certain about that. Certainly there have been none in the Center for Biologics. There's been at least three and possibly four at CBER, but --

DR. ABRAMSON: I guess I was most interested in what standards were established with respect to mandating Phase IV studies to capture these kind of data after accelerated approval.

DR. SCHWIETERMAN: Well, the standards are -- I don't have the preamble of the reg memorized on this, but I have reviewed it when we went through these different approvals.

There certainly are commitments that a company must make at the time of approval, and even more specifically, there has to be at least -- this is CBER's policy anyway, and I think that it holds for CDER as well, since we've had discussions about that.

The outlines of a protocol and often more than that, the endpoints, the projected accrual rate, the kinds of analyses that are going to be performed and so forth. Very often we get serial draft protocols, and the final protocol isn't finalized until several months after the approval because there's a lot to discuss in terms of the fineries and the details of that. But certainly the gist of the protocol has to be in there.

As to the language of the regs and the preamble itself, speaking with lawyers, it's not entirely clear how the issues would play out were the agency to begin withdrawal procedures because there are some legal issues about how you demonstrate, for example, that a sponsor is active with due diligence to pursue a particular commitment and so forth.

So I don't necessarily want to suggest that the regs are weak, but I just want to say that they're untested. Dr. Luckenbach points out, rightly, that there's at least one case in the Center for Biologics where we worked out a contract with a sponsor to engage in this

particular study, and that frankly is the spirit behind every accelerated approval because it's recognized at the time of the approval that there are many questions, in fact very many important clinical questions, which would obviously exist for this particular field and would be absolutely essential that there be an understanding probably in writing more often than not.

DR. ABRAMSON: Thank you.

DR. DALEY: Yes. Mike Daley from Sanofi-Synthelabo. The question actually brings together Dr. Brandt's presentation, Dr. Witter's, and that is what is an acceptable safety profile for an endpoint that really doesn't have a clinical read-out in terms of pain, et cetera? The pain and the structure modification may be independent, and there certainly are many patients that present that way.

So therefore, at the end of the day, if doxycycline is very effective in terms of, say, structure modification but may take four or five years to get significant pain relief, during that four- or five-year period of time, what is an accepted safety profile?

Because I think the analogy to NSAIDs, COX-2, is inappropriate because those are on a day-to-day clinical encounter trying to address the symptomatic problems of pain and mobility and lifestyle, et cetera, whereas

structure modification is almost like a prevention-type of thing. Trust us, take this, the disease will probably get better three to four years down the line. So what are the acceptable safety parameters that you have to do? They obviously have to be different than something that a patient is by definition going to take on a daily basis, whereas this is a promise that might deliver something in the future.

DR. ABRAMSON: Right. Okay. Any other comments or questions from the committee?

(No response.)

DR. ABRAMSON: The next item is an addition to the agenda, and that is we'd like to call on Dr. Lang from the Department of Radiology at Stanford University to make some comments about MRI.

DR. LANG: Dr. Abramson, ladies and gentlemen, I would like to thank you for the opportunity to speak to you here today.

Before I begin, I would like to take the opportunity today to thank my co-workers at Stanford University and the Departments of Radiology, Electrical Engineering, and Mechanical Engineering, all of whom have greatly contributed to this work. This has really been a joint effort.

In terms of financial disclosure, the majority

of our funding is from the Whittaker Foundation and the National Institutes of Health. We do also have some industrial funding from Chiron Pharmaceuticals, Genetics Institute, and Genzyme Tissue Repair for arthritis-related studies.

What I would like to show you here in the next 10 minutes is a summary of a longitudinal study in patients with early and intermediate stages of osteoarthritis using MRI. In the open public hearing, I would like to discuss very briefly some of the new MRI policy and new quantitative image analysis tools which lent themselves to be endpoints in clinical trials.

The challenge of our study, of our longitudinal MRI study, was to determine the prognostic significance of cartilage defects identified on the MRI, and for this purpose, we performed a retrospective review of MRIs in patients who had undergone repeat MRI imaging of the knee at Stanford University.

The time interval between the baseline and the follow-up knee MRI was by definition required to be more than 12 months. MRIs were obtained between 1993 and 1998. 1993 is essentially when we had the most basic of cartilage-sensitive knee MRI pulse sequences available.

We had a total of 43 patients who qualified for study inclusion with a mean time interval of 1.8 years and

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the range between 52 and 285 weeks. Our MRI imaging protocol is a standard knee MRI protocol with two cartilage-sensitive pulse sequences, a sagittal proton density-rated fast spinnaker sequence, and a T2-rated fast spinnaker sequence.

We read the MRI scans on a scale from 0 to 6, 0 being normal cartilage, Grade 1, signal heterogeneity, punctate foci of high and low signal within the substance of the cartilage but an intact-appearing cartilage surface, Grade 2 surface fraying, less than 1 millimeter into the depth of the cartilage, Grade 3 fissuring, Grade 4 thinning less than 50 percent, Grade 5 thinning greater than 50 percent, and Grade 6 full thickness cartilage loss.

This detailed reading, along also with analysis of osteophytes, of chondral sclerosis, of subchondral cysts, et cetera, which I'm not going to show here because in the interest of time, was performed in a very detailed fashion for multiple anatomic regions in the knee, such as in the medial femoral condyle, the anterior portion, central portion, posterior portion, and the same analysis in the lateral femoral condyle, medial tibial plateau, lateral tibial plateau, trochlea, and patella.

Let us take a look at the baseline data. With regard to the baseline data, we see that there's a lot of patients who have Grade 1 lesions, signal heterogeneity,

punctate foci of low and high signal intensity, with an intact cartilage surface, followed by fissures, and in fact less than 50 percent and greater than 50 percent cartilage loss.

On the follow-up data, mean time interval 1.8 years, we see that there's a strong shift towards fissuring and greater than 50 percent cartilage thickness loss. I would also like to point out that we performed a subgrading, Type A and B, which you can see here, 1A, 1B. Type A is if the lesion was less than one square centimeter in terms of area. Type B was when the lesion was greater than one square centimeter in terms of its size.

These are some representative case examples of what we encountered. The patella -- actually, if we could have the lights a little down? Thank you.

The patella cartilage. The normal cartilage has intermediate signal intensity, joint fluid is bright, and you can see here punctate focus of high-signal intensity and low-signal intensity in the median region of the patella with the completely-intact cartilage surface.

What happens in this case 13 months later? 13 months later, we see that this has evolved into a fissure, extending across the cartilage. Another example. Punctate foci of low-signal intensity and high-signal intensity here in the medial femoral condyle, the cartilage surface is

intact on MRI. This is the follow-up in this case, 17 months later, and you can see here that this has evolved into full thickness cartilage loss at Grade 6A, less than one square centimeter in size.

Another example. Signal heterogeneity in the medial femoral condyle here on a coronal MRI image, and 1.5 years later, note that the patient had an ACL graft. At the time of initial presentation, this patient had an ACL tear, and 1.5 years later, you see that this has evolved into full thickness cartilage loss with normal adjacent cartilage.

Another example. This is a patient who at the time of baseline scan had an area of less than 50 percent thinning in the posterior femoral condyle. Notice the normal thickness cartilage further anteriorally. The size was greater than one square centimeter, Grade 4B. On follow-up scan, the cartilage is completely absent. This has progressed into a Grade 6B full thickness cartilage loss.

So with regard to Grade 1, signal heterogeneity with an intact cartilage surface, we found that 25 percent of the lesions did in fact not progress. These may be stationary. 25 percent reverted back to normal. This is the most likely explanation for this, we think, is that the initial observation was an artifact, and I'll discuss this

in a second. Possibly this could also be a sign of in this very early stage of osteoarthritis offering a repair mechanism. We don't know the answer to this.

13 percent of the Grade 1 lesions increased in size within the same grade. That means from a 1A to 1B, they were larger in size, and 37 percent progressed to a higher grade. Ball park 50 percent of these early lesions progressed to a higher grade detected by MRI.

Now, were there any risk factors for more progressive, for more rapidly-progressive cartilage loss? Yes, there were. First of all, no specific grade lesion of 0 to 6 had a predilection for more rapid progression. However, patients who had meniscal tears at baseline had significantly greater risk to progress to a higher grade of cartilage loss on the follow-up study. Similarly, ACL tears were borderline significant, even though the majority of these cases had in fact undergone ACL repair.

Now, were there any regional differences in terms of the rate of cartilage lost, and when we look at the anterior medial femorotibial compartment, no. Post-femorotibial compartment, no. Post-femorotibial compartment, no. However, the central portions of the medial femorotibial compartment were significantly different, which we think is a reflection of higher biomechanical stress in this portion of the medial

femorotibial compartment.

What was amazing was the anterior lateral femorotibial compartment was also significantly different. We didn't understand this finding. When we went back to the original data, we found it was significantly different because in fact it would not progress. Relative immunity which may also be a reflection of lower biomechanical load applied in this area.

What are the limitations of the studies? There are multiple limitations to this work, and I want to point out that this is really a retrospective study of first attempt at getting longitudinal MRI data in patients with OA. We have only limited clinical information available on these patients, and many of those, we don't know if they're symptomatic or asymptomatic. Again, the primary inclusion criteria was the MRI.

Second, only a small number of patients studied. This cannot compare to a study like what Dr. Brandt just presented a moment ago. We would like to perform this type of study with high-resolution MRI pulse sequences to characterize these lesions even better, and ultimately you would want to have histologic correlation in terms of what these lesions represent.

In conclusion, we feel, based on the results of this preliminary study, that MRI can detect progression of

cartilage loss within a short observation period, ranging between one and two years.

Signal heterogeneity of the articular cartilage with an intact cartilage surface is frequently observed on knee MRIs. Approximately 40 percent of these areas progress to a higher grade of cartilage pathology over one to two years.

Meniscal tears and ACL tears predispose to more rapid progression of cartilage loss, and very importantly in our opinion, cartilage lesions in the central portion of the medial femorotibial compartment show more rapid progression, which we think is a reflection of biomechanics and which has led to some new work which I will show later, trying to fuse MRI with biomechanics.

I would like to thank you for your attention.

DR. ABRAMSON: Thank you very much.

Dr. Brandt?

DR. BRANDT: Those are very nice pictures, and you certainly make a point. But I think one of the next-to-last slides where you discuss limitations is terribly important. It has to do really with the specificity of these lesions in older people.

Most osteoarthritis is asymptomatic. Osteoarthritis in older people from a pathologic standpoint is ubiquitous, and most older people with joints like that

don't have trouble. They don't seek medical attention for their problem. They don't need doctors.

So the question is this, that those were, I guess, patients that you looked at. They may have been symptomatic or asymptomatic at the time you studied them as you point out, Dr. Lang, because they were selected on the basis of MRI, but they got into the system presumably because they had knee pain at some point.

DR. LANG: Yes.

DR. BRANDT: They're older individuals for the most part because they have osteoarthritis, I guess. The question is, what do these mean in terms of clinically important osteoarthritis? Are we likely to find the same sorts of abnormalities in absolutely asymptomatic people of a similar age?

DR. LANG: I agree 100 percent with your comments, and I really appreciate them. I can tell you, based on clinical experience, reading MRIs in average patients, we do several thousand knee MRIs per year at our institution, you will not see these abnormalities that I described here in a "normal knee" or a knee that just has an acute meniscal tear or any type of pathology like that. You will not see that.

However, clearly with regard to the study, we do have the major bias because you would hypothesize if the

patient has a baseline MRI and comes back for follow-up MRI, very likely the subject was symptomatic at the time of follow-up. Otherwise, he or she wouldn't have had the follow-up MRI. So clearly, that is a bias.

I think the power of this study and the philosophy, the amazing result is that with this study that had so few patients, we weren't able in fact to detect an effect, and, second, our patients were by no means stratified at all, but nonetheless we were able to detect an effect.

So I think that once we can do an NIH-funded study, follow patients longitudinally with these techniques, we may even be able to see much stronger effects, and one of the things that really intrigues us is in fact we would like to cut down this observation period and look at patients at the six-month follow-up with a well-defined study population and clearly-defined and stratified patient groups.

DR. ABRAMSON: Dr. Dieppe?

DR. DIEPPE: Thank you. Just to say, to begin with, that we have rather similar findings to you in terms of the distribution foci and also in relation to the importance of meniscal lesions seen on MRI and that ordinarily all the people we see who get progressive changes on x-ray studies, where we've got MRI done as well,

they've got meniscal lesions.

The question I have for you is sort of to make another point, I think, really, which is to say that I presume that in those cases where you show very pretty pictures of focal lesions, where there can be complete cartilage loss just in one focal section, with the articular cartilage either side, is normal, that there will be no change in those cases on the x-ray joint space.

DR. LANG: Again, I have to point out that in this study, we have limited clinical and x-ray information available from this perspective. I have to put a big caveat in front of my answer.

I can tell you that we have seen several cases in the study that have these focal areas, in fact a full thickness cartilage loss, but over an area of maybe one or two square centimeter, where in fact the x-ray was negative. We would not detect those and done with the semi-plex, with the proper technique, but nonetheless we really need to get more data for this to confirm this, and a big caveat in front of the statement.

DR. ABRAMSON: Dr. Dougados?

DR. DOUGADOS: Yes. I would like to comment that it is possible with MRI to observe changes in a short period of time, but I would like to ask a question.

First of all, the machine. We're to use a

conventional one which is quite money-consuming, and another one, which is dedicated for the lower limbs, which might be more useful in practice and to conduct clinical studies.

The second one is the regimen. Are you using a IV injection of gadolinium, yes, or no, because it's much more complicated if you have to inject something with an IV injection. It's more expensive.

The third thing is the way you analyze because you have three main characteristics. If you focus on the calculated effect, the organization, the dense and the size. That is the reason why the French use the arthroscopy for composite index, range from zero to 100, taking into account the inflammation. Otherwise, I have not understood when you have a patient which is with a defect of Grade 1A, switching to 2B, and in the same knee for the same patient, a defect of 2B, going down to 1A.

Is it a progression or is it not a progression? That is the reason why we have need for composite index of this kind of thing, and I remind you that there was a discussion of several groups of people dealing with MRI at the previous ACR meeting in San Diego to discuss the best way to analyze this defect, and, finally, evaluation is also important because we have compared the sensitivity to change using the standardized response mean over a one-year

period of time, comparing x-ray, arthroscopy and MRI, and we do agree that we found that the joint fragility -- a good sensitivity to change using MRI, but in other words, in your study, I have not understood what was the -- was it a different period of time by patient? Some patient have only one year and other patient have half because sensitivity to change is closely related to the duration between the two visits.

DR. LANG: In terms of your first question, all of these imaging studies were performed at 1.5 tesla, which is the standard whole-body MRI imaging systems. I think for later, these are -- a lot of these, I would say, are early to intermediate stage OA.

For later stage OA, I think the dedicated extremity scanners can be quite attractive. Professor Alashya in Paris has done a tremendous amount of work on this and really pioneered along with groups in the United States. But again everything that I have shown here is based on the 1.5 tesla scanner.

With regard to your question about gadolinium, no, these scans were not performed with gadolinium. That was the technique initially described by Deb Burstein as a means of getting at proteoglycan or glycosaminoglycan content in the articular cartilage.

We are currently performing a Phase II clinical

trial using this, among other techniques, where we in fact tried to get quantitatively changes in glycosaminoglycan concentration.

The third question, I'm well aware of the French grading. I think that's a great staging system. I read the papers, and in many ways, the grading that we perform here is quite similar. The difference is that we do not derive a total score at the end. We look at the individual.

You saw the per-rating individual in multiple different regions of interest, anterior, central and posterior, et cetera, and what we did is in each region, we would score each lesion individually. If we saw two lesions within the same region, we would go by the lesion that had the higher score, that had the higher grading. We would look at what happens to this longitudinally over time.

And again I have to point out this is sensitivity to change. This is a retrospective study. As such, we have no control in terms of the time of follow-up. We have an NIH proposal pending at this point, and hopefully we'll get it, trying to study patients at well-defined time intervals, longitudinally, over time.

DR. ABRAMSON: Thank you, Dr. Lang.

I think to move the discussion along, I'd like

to ask the committee members to make comments, if they have them, but let's not pose any further questions to Dr. Lang about his presentation.

So Dr. Elashoff, do you have a comment?

DR. ELASHOFF: Well, it was a question, but it has to do with the issue of what kind of blinding. Do you know when you rated the -- these two are one patient, and which is pre and post, and it has to do also with the degree of agreement between different readers which is important in evaluating studies like this?

DR. ABRAMSON: Thank you.

Dr. Brandt, do you have a comment?

DR. BRANDT: Yes, a small point to follow up on Paul Dieppe's comment. Presuming that the x-rays were normal, and those showed small focal lesions in articular cartilage, you said MRI is clearly more sensitive than plain radiography, but not -- I don't think we could presume, though, nonetheless, that radiographs would be normal with regard to joint space.

There's a lot of variables. Five degrees of flexion in my knee narrows my joint space 17 percent, and patients who have little symptoms, that's why it's so important to have rigorous standardization of positioning if we're going to use plain radiography.

DR. ABRAMSON: Thank you.

I'd like to move now to Dr. Kent Johnson from the agency to talk about transition and preamble.

DR. JOHNSON: I'm not sure what that title means. I'm only going to take five or 10 minutes to do this transition and preamble.

You can hold off on that for a second, Tony, okay?

I'm going to take off a bit in the spirit of Jim Witter's talk and try to kind of entertain the greater vision here a bit. We do have a lot of analytic challenges in the paradigm that we're considering for osteoarthritis, and that will be the subject of a lot of the questions, a lot of the discussion today.

The document you have is the second draft, as Jim pointed out. It's a tri-center draft. It's been through, you know, Drugs, Biologics, and Devices. There will be further drafts, I'm sure, but I think more importantly, it's kind of an attempt at a concept paper, and in that vein, I think it's important that we try to continue to work toward concordance with other regulatory bodies, particularly the EU, which is why we've been actually informally doing a lot of collaboration back and forth over the years, and hopefully it's not surprising that the two products eventually become pretty concordant.

Finally, I want to just show one slide that's

kind of a historic view from the past -- go ahead, Tony --and where we may be heading. As most of you know, in the prior decade, we had a very empiric approach to osteoarthritis as we did with rheumatoid, as a matter of fact. We had four variables. It was never entirely clear what the fourth one was in osteoarthritis, but pain and the investigator global and patient global were the other ones.

This was fundamentally a data-driven informal process that had occurred within the FDA as a function of earlier non-steroidal NDAse, probably five or 10 of them over the previous decade.

We simply looked at a trial and evaluated whether three out of four of these variables actually were statistically significant. No multiplicity considerations were taken into account. This complication was always kind of in the backdrop, and the problem has always been and continues to be with multiplicity, that the correlation structure can only be determined after the trial is done, essentially. So it's very hard to prespecify what multiplicity adjustment you would take if you felt obligated to take one.

There are a number of people actually in our statistical group, Dr. Houke and his colleagues, who are trying to sort out this problem, and hopefully they'll give us an answer here in a few years.

In the interim, in the early '90s, OMERACT, I think, was a big help in sort of consensus-driving concept. The notion that, you know, the adequate assessment of the disease itself requires attention to certain domains, and those domains in fact we've incorporated in our guidance as pain, function and patient global, and the fourth domain was structure for trials over a year's duration.

Again, we still have the multiplicity problem, and there's always the issue of certain covariates that need to be attended to, and then it's possible actually to entertain this particular measure as a fourth primary measure, and we've done that on certain occasions, and the subject for today is structure.

You know, in my mind, and I think in the mind of a patient, as you sit there looking at a crummy x-ray and somebody who's been symptomatic, considering a total joint replacement, the structure comes across as much more than a surrogate. I mean, there it is. That's the disease. It's a nice graphic representation of the disease.

One of the analytic issues that we have to deal with is how accurately joint-space narrowing becomes a surrogate for structure. I mean, it's not hard to buy into the notion that structure may be a valid surrogate for eventual clinical improvement, and in fact, that's what

we're proposing, using this accelerated approval statute that's already been talked about.

Obviously, as Bill Schwieterman just pointed out, the timing of what one does Phase IV is critical, and I mean the diligence is important and so on and so forth, but obviously if you have a product that succeeds dramatically by structure, you're going to have a hard time continuing a trial into Phase IV with patients whose x-rays look crummy, and especially if you're convinced that your hypothesis that structure will eventually transform into clinical benefit is true.

I mean, if you really believe that, you're going to probably be inclined to drop patients out of the placebo arms if their x-rays look lousy, and in fact, that's one of the topics we're going to discuss. It's the fourth point under "Endpoints" in these various questions that we've put on the agenda.

There's a lot of analytical work going on in the realm of how to quantify and how to actually rank surrogates. If people are interested, this is mainly in the AIDS literature and in Statistics in Medicine journal.

There's a fellow by the name of Prentice back in 1989 who was the first to try to quantify the issue, and he just presented a surrogate marker concept in an all or nothing fashion, and fundamentally, the test for the

validity of a surrogate marker was whether or not the null hypothesis of no treatment difference in that marker was also a valid test of the null hypothesis of the clinical endpoints. So you either had it a 100 percent or you didn't have it at all.

More recently, there's been attempts to try to rank surrogate markers, and in fact, the recent work in the AIDS world, where you combine CD4 and viral load, there are recent articles that describe this, and it is argued that you can account for 70 or 80 percent of the eventual clinical outcomes in that scenario.

However, the ability of a marker, if it ranks very high in some kind of scheme like that, is a necessary but not sufficient as it turns out, not sufficient criteria for the marker to be valid, and the reason for that is, as Jim alluded to, if your drugs have unexpected negative consequences when they're tested in an interventional study, then the benefit on the marker and hence on the clinical endpoints might be undermined or counterbalanced by some toxicity of the drug.

In any case, I think the concept of using joint-space narrowing in the accelerated approval scenario is not controversial. How much joint-space narrowing you need, how you orchestrate your Phase IV validation and so on, those are the critical points.

Most in this room, I think, are probably aware of these two initiatives. The OARS Group, Osteoarthritis Research Society, has been data-driving a process to put together an OA knee responder index which should be very useful. I believe Maxime was telling me that the results, the actual analytic results of this initiative are going to be presented at the next OARS meeting in Vienna in September. Yes. So that will be very helpful.

The second is a new initiative on the part of Steven Katz and NIAMS and a number of other centers at NIH, as a matter of fact, so-called biomarker initiative. This is just in its formative stage. This is a fully-public initiative at this point in time. Greg Downing, who may be in the audience, is the point person for this at NIAMS. I believe they have -- is your web site up yet, Greg? Is your web site up and running? Yes?

DR. DOWNING: Yes.

DR. JOHNSON: Okay. So you can give him a call and get that information, if you'd like.

The scope of this project is not yet fully determined. There's going to be a big meeting this winter where sort of the intellectual architecture of the whole thing is going to be discussed, and hopefully a consensus will be reached.

This is involving academic centers that have an

interest and industry research programs and regulatory involvement, and, finally, one could sort of have a vision of the future where we could entertain certain other endpoints that are logically, you know, very attractive.

I think it may be that the analytic challenges might become less really as we improve in our ability to impinge in a major way in this disease. I hope that's the case.

I often envy oncology in some ways. I think, you know, the tumor's either gone or it's recurred, and I'm sure it's more complicated if you're actually working in the field, but from the outside, it seems simpler.

And, finally, I think it's important that we continue this ongoing rapport. I think that the rheumatology clinical community, both academics and industry and the regulatory people, have a history of ability to accomplish and push the field forward. So it's in that spirit that I thank everybody for coming today, and I hope we have a good discussion.

DR. ABRAMSON: Thank you, Kent.

Are there any questions for Kent Johnson?

(No response.)

DR. ABRAMSON: Thank you very much.

All right. I guess we can go right into the questions that are listed under "Design Endpoints," and the

first question, which focuses on structure, we can also, I think, in the comments talk both about the x-ray and possibly the MRI as endpoints.

So let me just read the question. "Joint-space narrowing: if a minimum effective size is required, a minimally clinically important difference, how should this be defined?"

Dr. Brandt left the room.

DR. SCHWIETERMAN: I just want to point out that there's a typo in the guidance document. Instead of less than 50 percent, it should be greater than 50 percent about page 3 or 4, and it's an example. It's not meant to be the cut-off. It's meant to be a quantitative example of how the agency believes you might actually judge for a particular product the threshold.

We wanted to -- page 7. Excuse me. I don't want this point to be lost because it's not as if the agency believes anything greater than 50 percent is --

DR. ABRAMSON: Right. The line is, "In general, sponsors seeking this claim should anticipate relatively large changes, that is greater than 50 percent, in slowing joint-space narrowing relative to the control arm." On page 7.

Okay. Marc, do you want to kick off on this?

DR. HOCHBERG: Well, I actually have a

question, and I think a point of discussion, so we're all on the same page. Are we discussing this in the role that structural change is the surrogate variable to the clinical outcome of total joint replacement?

Am I correctly understanding what has been inferred by Dr. Witter and what I'm implying from what your talk is, that the corollary of death here is joint failure. Joint failure is marked by a joint replacement, and that we're looking at structural change in an imaging procedure as a surrogate for joint failure? Am I understanding you correctly?

DR. JOHNSON: I'll let Jim comment, too. No, we have not specified total joint replacement. We've actually discussed the utility of that measure which is tricky, but we've only specified that you need some kind of clinical substantiation that your joint-space narrowing translates.

DR. HOCHBERG: I'm not suggesting throwing joint replacement as an outcome variable. What I'm trying to do is understand the presentations this morning in the context of the discussion that we're now going to have, that structural change is a surrogate for the ultimate outcome of joint failure, which can be marked by a joint replacement in some people who have access to health care and insurance to pay for the joint replacement.

DR. JOHNSON: Well, I'm sure if you designed a trial that used -- I don't know how to answer this sort of in the nebulous abstract. If you design a trial that has a total joint replacement as the endpoint, it would be considered a win if it succeeded.

DR. HOCHBERG: Well, I guess I'm not explaining myself. Sometimes we design -- in cardiovascular disease, for instance, we might have an endpoint, a surrogate, for death. Okay. We just heard yesterday in the news about a trial of naldactone in severe congestive heart failure that reduced the death rate.

Well, maybe there's a surrogate for death in that setting. For instance, injection fraction. Okay? That's an example.

So here, what we're looking at is structure of the joint as a surrogate for some clinically-important outcome which is joint failure. Now, I'm not proposing that we discuss trial design for decreasing the rate of joint replacement, but what I'm trying to do is understand the structure in the context.

Is structure being looked at as a surrogate variable or is structure being looked at as a clinically-important outcome by itself?

DR. SCHWIETERMAN: Let me try to answer that. I think all three of us could give variations on that.

I think you've hit on a very important point, and I think you have given an example of a clinically-important outcome, but I think that your comments perhaps need to be amplified. There are other clinically-important outcomes for which joint-space narrowing could act as a surrogate.

For example, it could be patient function, whether that patient's able to open jars, engage in the normal activities and so forth.

Of course, there are degrees on the continuum down, and joint replacement would be the ultimate, and if it's helpful to think of those kind of outcome measures, then I think you should do it, but the agency would not necessarily require in a Phase IV study that you demonstrate that by virtue of preventing joint-space narrowing, that you would thereby prevent those patients down the road from having their joints replaced because there are smaller benefits that we believe are important to the patients and thereby to the public by which you could justify accelerated approval for this.

The other example, of course, are perhaps new classes of products coming down that are dissociated from pain and signs and symptoms, in which case you could simply use joint-space narrowing as a surrogate for perhaps future evolution of clinical signs and symptoms, and that's a

debatable point, but I think it's one that's been raised in this committee before.

So I think we agree with the essence of what you're saying, but we would not limit it to those kind of structural outcomes, but if it's helpful to think of this in terms of long-term outcomes, then, yes, that is the ultimate bad outcome in many respects.

DR. ABRAMSON: Dr. Yocum?

DR. YOCUM: I guess, just having attended a rather interesting conference on osteoporosis and hearing about the T scores that we had relied upon so much over the last two years that appear to be able to be thrown out, and what we relied on is basically bogus or at least that's what's suggested, I'm concerned about joint-space narrowing, and much of the discussion I've heard not only on MRI as well as the various views and having been involved in Ken's studies, it looks like it, one, isn't well standardized.

It hasn't been widely used, I'm not even sure, from the statistical standpoint of the long-term benefits of this, and then in the standard clinical practice, the patients who come to me have lost already a lot of joint space.

Are we really beating a dead horse here? Is there ultimately some benefits to this down the road? I

don't see. Is it a bright and shiny star? Maybe I'm being very naive here, but it looks very negative to me.

DR. JOHNSON: The believers -- I think it's seems very analogous to the AIDS situation, you know, 10 years ago or whenever, you know, the CD4 story started coming around, and, you know, there are believers in that, and it turned out CD4 in isolation was not a very good surrogate marker, but there were -- you know, the NCI trials were ongoing when the CD marker differences were evident, and the drugs were approved, and the trials validated it as it turned out.

So I'm not sure. I think Marc's question -- were you wondering if we were asking what is a clinically-important symptomatic outcome? Because that's sort of a whole different debate.

DR. HOCHBERG: No. I was asking in the context of whether the agency considers structure modification to be in and of itself a clinically-important outcome or a surrogate for another clinically-important outcome which I would choose not to define because I don't want to further muddy the waters.

I mean, we've published data and other people have published data to show that severe radiographic change predicts people going on to having a clinically-important outcome, such as a total joint replacement, independent of

pain, and you might infer from that that if you prevented the development of severe structural change, you might reduce the risk of total joint replacement in the future.

But my question was just, is structure itself a clinically-important outcome or is it a surrogate?

DR. JOHNSON: Well, you can infer that, but you might be incorrect if your interventional trial in fact failed. I mean, I think a lot of us believe that structure has a certain cache to it, a certain face validity. It's there. It seems real. But it's not a symptom. I mean, the patient doesn't feel the structure of the joint. I mean, it feels pain, I guess.

So I don't know. My perception is what the agency's doing is that it's meant to use the accelerated approval in exactly this kind of setting, where there's a major reason epidemiologically and everything else to suspect this, but, you know, it should be proven, and it needn't be proven preapproval. It can be proven postapproval.

DR. ABRAMSON: Dr. Dougados?

DR. DOUGADOS: And I do agree with Marc when he said that we consider that structure is more important to consider for the patient. The question is that usually when we are conducting these kind of studies, we're checking serial change, Grade 4, something like that.

In the ongoing clinical trial, we are looking at .1 millimeter of change. So what is the clinical relevance of this .1 millimeter change? Assume that is the reason why we're having so many discussions between the agency and the academic, because from an academic point of view, the serial change are clinically relevant, but in the ongoing clinical trials, we are not checking the serial change. We are checking small changes, such as the MRI, to check the .1 millimeter during a trial, and it's sufficient to consider this kind of compound with which we will be able to have a .1 millimeter difference between the placebo and the active compound.

DR. ABRAMSON: Right. I think that's getting at the spirit of the Question Number 1, where I think the agency would like us to focus. It begs a couple of questions, such as whether the x-ray or the joint-space narrowing is in fact a good surrogate for outcome, but I think that's kind of implicit in the question.

It also raises the issue, the harder question, is what is the face validity of the technology that we currently are using, and I think one of the presumptions in the question is that the technology does have some validity, but I think that's open to some debate.

But having said that, I think we should focus our attention on if we look at the techniques that are

currently available, on which there are already ongoing studies, such as the semi-flex position and perhaps the MRI as a secondary issue, what are clinically relevant changes that should be the standard in clinical studies?

Jim or Ken, does that capture the sense of what you're getting at in Question Number 1?

DR. WITTER: Yes, and I think really what Marc's comments were, were pretty much right on the mark, and I think what we'd like to do, at least from my perspective, is kind of throw that back at you as the question.

If a compound, for example, comes in, and we're viewing it as this endpoint of structure modification as a surrogate, what should we do? If we don't view it as a surrogate and in fact as the endpoint, then what do we do?

I mean, I think we need to hear some of that discussion and that's part of the point of today. So.

DR. YOCUM: But I guess my point is, is that I heard from the MRI that meniscal damage, medial compartment damage, is associated with what sounds like a significant risk of total knee replacement down the road.

However, I have heard no data here that one millimeter of joint-space loss, okay, narrowing is going to result in X number of total knee arthroplasties which is important to the patient, which gets to what Mark is

talking about. Is it a valid surrogate?

And I'm not hearing any data that joint-space narrowing directly correlates to the need for a total joint because that's what my patient is interested in.

DR. JOHNSON: Yes. I think Maxime has data in that regard, but I think his report is the only piece of data, and it's true that the epidemiology is not as strong as in hypertension or cholesterol or something like that.

But the face validity, I think, is also different, which gets to Marc's issue, that, you know, maybe you could argue that you should approve just on the basis of the x-rays, and we'll look at the clinical information, and we'll make a sort of risk/benefit judgment, you know.

DR. YOCUM: But for the patients, you know, the glucosamine story, I mean without pain changes and saying, well, 30 years down the road, you're going to have a 10-percent less chance, are patients really going to take these medicines for an extended period of time, and it would be nice to have a more stronger marker.

Now, meniscal tears, boy, there, they've had damage and something is there, but again I'm just not hearing the data I'd like to hear.

DR. ABRAMSON: Right. I think part of the conundrum is we're in a phase of investigation. We are

DR. DIEPPE: Well, we have some data in answer to Jennifer Anderson's questions which rather reinforces, David, the outcomes worries, in that over three years of progression of OA in a large cohort we looked at, there was no correlation between structural change and change in pain and disability.

Now, I think there are two problems here that we haven't really raised which we need to have out on the table in relation to this. One is the long time frame that we might be involved in.

I believe that joint-space narrowing will be a surrogate of serious clinical outcome, but I think it might take an incredibly long time, and then the whole issue of relative gain that you're making over short time period versus long time period is a very complicated issue for patients, and I think we have to recognize that there might be short-term loss for long-term gain, and how do you deal with that.

And I think the other issue that has to be out on the table is we're largely talking about older people who often have comorbidities, and if you're starting to talk about very long time points to get an outcome, what else is happening in terms of comorbidities and other systems during that time frame, and in following our own cohorts of patients, and we do have some longitudinal data,

it's comorbidities that become much, much more important than what's happening with the osteoarthritis.

By comorbidities, I don't just mean physical or other organ endpoints but psychosocial factors, and they become the dominant factors to the majority of the people we followed prospectively. So I'm quite worried about the approach that says look at the short-term structural change.

DR. ABRAMSON: Dr. Hochberg, do you want to address the outcome? The epidemiology?

DR. HOCHBERG: Well, we've looked at some data from a "normative population," volunteers in the Baltimore longitudinal study on aging, who were not selected for the presence of OA, and we've found that in people who have normal baseline knee radiographs, when they have subsequent radiographs over time, on average, the joint space doesn't change, that the mean delta doesn't significantly differ from zero, while those who have OA at the baseline x-ray based on a Kellgren and Lawrence 2 or higher, their mean joint space does significantly go down over time.

In a separate analysis, and again this is all related to, you know, decisions that people make about doing interventions as well as access to health care, that people with more severe radiographic change are more likely to undergo joint replacement independent of pain.

DR. ABRAMSON: Does your data shed any light on the rate of progression of X millimeters per year in your follow-up of people who do progress?

DR. HOCHBERG: Well, it's pretty small. It was about .2 millimeters per year for those that had baseline osteoarthritis on average.

DR. ABRAMSON: Okay. All right. Let me just go back. Dr. Dougados, if you could make a brief presentation?

DR. DOUGADOS: Just to try to answer the question of the individual patient, what is clinically relevant, and we have conducted studies, the first studies we have conducted by starting to say that any structural change is clinically relevant, and from an epidemiological point of view, any structural change that is a change which is not related to a measurement error, and not because there was a noise when you are looking at the changes, and therefore we have conducted several studies in this, that is, with nothing to do with a clinical relevance but only to postulate that any structural change is clinically relevant, but we don't take into account the noise of the technique.

And we evaluated several techniques looking at -- I don't know whether or not you are aware of the blinded Alban technique, looking at the reproducibility of the

technique between two examinations, 30 times, and you are looking at the mean of the difference between the three evaluations, and then you are focusing on the standard deviation of the changes, and then you can calculate the noise due to the measurement error, and then you have a cut-off permitting to say after that in the study, if you see a progression more than X, therefore you can consider reasonably that this change is not due to measurement error but is due to the structural change.

In order to answer to Ken, we have evaluated the usefulness of the fluoroscopy concerning this cut-off. If we are using guidelines, not guidelines, fluoroscopy, not fluoroscopy, what is the consequences in the calculation in this cut-off?

You can see the answer. As an example, if you are evaluating -- do we have a pointer? James, do you have a pointer? Here, you see the results of the cut-off that is -- I need only one. Thank you.

DR. ELASHOFF: You'll need to read the numbers because we can't read them from over here.

DR. DOUGADOS: Okay. So the figures you can see or you can't see in this slide find the cut-off damage in the further study. If you see a change more than that, you can consider that the change is due to structural change and not due to measurement error, and if, as an

example, in knee OA patients, you are using guidelines, that is you trained the radiological team without fluoroscopy, and depending on the risk-taking, a change of more than 6 millimeter can be considered as related to a structural change and not to a measurement error.

So depending on the technique -- so, such cut-off is related to both the technique and the investigator. The senior investigator -- so, that's a possibility to try to get an answer. Yes, it's possible not to give a clinically relevant cut-off, but at least to pick a cut-off to avoid the measurement error.

That has been described in the psychological field, MID, minimum individual difference, or SDD, smallest detectable difference. That has nothing to do with the clinical relevance, but it has something to do to the face validity of what you are looking at.

We also conducted another study which probably would interest David. We forget this, and now we are looking at the predictive validity of a change in the joint-space narrowing in the short term, not an absolute value, and to look at the predictive validity, but what we are doing in clinical trials is a change in the short term. Is it predictive of something?

In the study, we have conducted something that is a gold standard, was not symptoms but requirement for

total hip replacement. So we have a cohort of patients with osteoarthritis in which we have conducted at baseline one evaluation, the joint-space narrowing. After one year of follow-up, another x-ray, so we can calculate the change in the joint-space narrowing within one year, and during the two subsequent years, we have calculated the risk for total hip replacement, and we have calculated this risk with regard to the changes observed during the first year in terms of joint-space narrowing, and you see here that the risk for total hip replacements was much more important in the group of patients with radiological worsening of more than 50 percent in terms of joint-space narrowing. But there was also an increased risk in the patients with radiological worsening over 25 percent.

Based on these results, we have confirmed the longer in follow-up. Another possibility is to say that in an individual patient, if we observe the change of at least 25 percent, we can consider that this change is clinically relevant and --

DR. JOHNSON: Were the average joint-space narrowing at baseline roughly the same?

DR. DOUGADOS: Not roughly the same. Not roughly the same because the Group D at the lower joint space with baseline -- that is, more you have an advanced disease, not -- you have a low joint-space width, more you

will rapidly progress the next year. The baseline value is predictive of the change during one year.

DR. JOHNSON: So you've got two risk factors essentially. One is the baseline joint-space narrowing, and the other is the rapidity of change?

DR. DOUGADOS: Yes. That is the reason why in these particular studies, it was better to pick up the percent of change than the absolute change because in the percent of change, you also take into account the baseline value. If you take the absolute change, it's less impressive than the percent of change.

So that is the reason why our proposition is if you want to have two cut-offs, the first one is -- and I can't give you the results we have applied in three-year placebo trial in hip, to say either to use the SDD technique, the smallness detectable difference, and then as an example, the cut-off is .5 millimeter. That's an absolute value. That is, if you observe a change of at least .5 millimeter, therefore you can consider that the change is not related to a measurement error but is related to a structural change, or to say that if you observe a change of at least 25 percent, that is clinically relevant, and it's quite -- we have conducted a three-year placebo trial, and after three years of follow-up, we have roughly 50 percent of the patients who have the progression of at

least 25 percent or 50 percent of the patients with progression of at least .5 millimeter.

DR. ABRAMSON: Dr. Brandt has a question.

DR. BRANDT: Yes. Kent Johnson's point, I think, is very important. Maxime, what was the mean joint-space width at time zero in Group D and in Group C?

DR. DOUGADOS: The mean for the one group of patients was 2.3 millimeter.

DR. BRANDT: Group D and Group C.

DR. DOUGADOS: Yes, but I don't remember the exact -- I can't --

DR. BRANDT: I would suspect there was almost no joint space in the second Group D.

DR. DOUGADOS: There was a low risk value.

DR. BRANDT: Yes.

DR. DOUGADOS: Yes.

DR. ABRAMSON: Okay. Dr. Dieppe?

DR. DIEPPE: Maxime, I think what you're showing there is what we've perhaps, if I may so, known for quite a long time, which is there's a very small subset of people with bad hip allay who progress rapidly, and it is a small subset, and it's well known.

I would challenge you that this is not generalizable to the knee joint.

DR. ABRAMSON: Dr. Brandt?

DR. BRANDT: But this is different from the syndrome or the picture of rapidly-progressive OA of the hip or rapidly-progressive OA of the knee that Michel Lequesne has described, where they're starting with a fairly substantial joint space with things that disappear before your eyes. That's my point, is that those Group Ds, I suspect, at zero time had already lost everything, and to lose 50 percent of nothing is not trackable.

DR. DOUGADOS: In fact, in accordance with the definition of Michel Lequesne, you're right. The primary rapidly-progressive OA of the hip is of a normal joint-space width at baseline, but this kind of patient, and I agree with Paul, that's the secondary rapidly-progressive OA which is completely different.

But even that, we were unable in this study to find an ability to determine in the change in the joint-space width; that is, this Group D is in fact the right part of the curve, but we have no ability to determine. We were unable to pick up the particular population.

DR. DIEPPE: In the knee?

DR. DOUGADOS: In the hip. That's the hip.

DR. ABRAMSON: Dr. Anderson?

DR. ANDERSON: Yes. I was just wondering whether the joint-space narrowing measurement was known when it was decided whether or not to do the hip

replacement.

DR. DOUGADOS: For the hip replacement? That's a weakness of the study. Of course, that's a multi-center French study, and the decision for total hip replacement is based on both things, the clinical symptoms and problems with structural, not the changes. The surgeon would do the decision for the surgery and only one value, that is last value of the pelvic x-ray, but he was not aware of the changes.

DR. ANDERSON: Oh, okay.

DR. DOUGADOS: Do you see the difference?

DR. ANDERSON: Yes.

DR. DOUGADOS: But I agree with you that the value of the study, he was aware --

DR. ANDERSON: He was aware?

DR. DOUGADOS: -- of the last value.

DR. ANDERSON: So that did play a role in making the decision?

DR. DOUGADOS: Yes.

DR. ANDERSON: It would have been better --

DR. DOUGADOS: Usually surgeons in my country do not propose intervention with normal joint-space width.

DR. ANDERSON: Okay. Well, yes.

DR. DOUGADOS: In my country.

DR. ANDERSON: Yes. No. I was wondering. I

mean, in some places, it's done based on only the symptoms or function.

DR. DOUGADOS: In terms of function? I can show you. There was a huge difference in terms of symptoms between the patient with or without intervention concerning the last observation of the symptoms.

DR. LIN: Excuse me. Before we take that slide off, just a question. You said D at baseline was different, lower than the Groups A, B and C, but among A, B and C, were they different at baseline?

DR. DOUGADOS: I don't remember. I have to check that.

DR. LIN: Because that in themselves have some information looking at those three curves there.

DR. DOUGADOS: I am aware that when we conducted the analysis, to pick the predisposing factor, the baseline predisposing factor of total hip replacement, but without regard to the change during the first year, the baseline value of the joint space was predictive, taking into account the information coming from symptoms was predictive of total hip replacement by itself, and the cut-off, which has been -- I think it was 1.5 millimeter. That is all I remember, but I have not this information that the joint-space width with the data, but I can check that.

DR. ABRAMSON: Dr. Brandt?

DR. LIN: Excuse me. It was my understanding that Dr. Hochberg has some data that's similar to this. You said earlier that you had a group of patients that you looked at the knee, that the joint-space narrowing has some implications on the knee replacement down the road. Is that similar to this?

DR. HOCHBERG: We looked at baseline knee x-rays which were for baseline, and the x-rays which were obtained during a restricted time period among BLSA participants who had also completed a standard pain question, and then we looked at subsequent knee surgery and found that those who had Kellgren-Lawrence Grade 3 or 4 or radiographic change at baseline were at greater risk of undergoing subsequent total joint replacement, even after adjusting for pain and BMI and age, than those with Kellgren-Lawrence Grade 2 changes.

So one can infer from that that the part of becoming a Grade 3 or a Grade 4, as Dr. Brandt didn't show but had in his study, as having more severe radiographic change, including joint-space narrowing.

DR. ABRAMSON: Dr. Brandt?

DR. BRANDT: Maxime, how did the measurement errors differ between Group D, say, and Group A?

DR. DOUGADOS: The measurement error?

DR. BRANDT: It was taken into account.

DR. DOUGADOS: When there's a measurement that is a cut-off coming from the progression, yes or no, that is related to the technique you have used, the Blount and Alban technique?

DR. BRANDT: The variability with repeated measurement when there's very, very little joint space as opposed to having three millimeters or four millimeters.

DR. DOUGADOS: Yes. That is an advantage of the Blount and Alban technique because when you are evaluating this cut-off that is .5 millimeter, you are evaluating the patient with a broad range of the disease, that is in this study, from one millimeter that was the lowest joint space with that entry up to 4.5 millimeter or 5.6 millimeter, and the noise was quite similar, was not more important in the lowest -- the more severe disease and the less severe disease. That was the question.

And I agree with Marc because here are the predictive factors of requirement for total hip replacement, and the Kellgren and Lawrence score was taken into account in this material and analyzed, despite the fact that we have also other demographic data, sex, the female, and level of symptoms, pain, and the index.

DR. ABRAMSON: Kent?

DR. JOHNSON: So those are all as a consequence of a multi-variate analysis? They all still remain as

independent risk factors?

DR. DOUGADOS: Yes.

DR. JOHNSON: And if you add joint-space change in the first year into the model --

DR. DOUGADOS: Less.

DR. JOHNSON: -- do some of those drop out?

DR. DOUGADOS: Oh, to add the change in the joint space with in this model --

DR. JOHNSON: Yes.

DR. DOUGADOS: -- I am not sure we have done that. We have two different questions. Are the baseline characteristics of the patients predictive of requirement for total hip replacement, and here are the results of this material analysis, and the second complete difference in analysis were are the changes within the one year predictive of subsequent. That is that I have shown. But I am not sure that if you include the changes in this to take into account the demographic data, I don't know.

DR. JOHNSON: Yes.

DR. ABRAMSON: Okay. Thank you.

Why don't we come back to the question that was posed? I guess we have a little more data, but things are still kind of murky. We have data from the hip but not from the knee. The data, as you suggest, over 50 percent, at least in your study, is a -- I'm sorry? Over 25.

Fifty, definitely.

DR. DOUGADOS: Fifty-five, 25.

DR. ABRAMSON: Let's just ask people now to what extent can we address Question Number 1, given the discussion we've had up until now and making the assumption that these are the instruments that we have to assess? Do people on the committee have comments with respect to what is a clinically-significant change of joint-space narrowing?

DR. SCHWIETERMAN: Dr. Abramson, I'd just like to clarify the question a little bit to specify the regulatory framework by which accelerated approval might be given.

Accelerated approval is reserved for serious and life-threatening diseases, of which the agency believes debilitating RA is one. But the surrogate, by definition, is an unvalidated surrogate because if it were a validated surrogate, the product could get out and out approval.

So by definition, it needs to be an unvalidated surrogate reasonably likely to confer clinical benefit to the patient over the long term. So the standards by which the agency then goes with this is to say what is reasonably likely to connote benefit? Perhaps that will help the discussion.

DR. ABRAMSON: Right. So I guess the analogy

might be myocardial infarction and coronary angiography. What is a reasonable radiographic surrogate for myocardial infarction, and what I think the panel is struggling with is we don't have the validated arteriogram. We have less good imaging techniques in current state.

So anyone want to take a crack at addressing the question? Well, go ahead, Dr. Anderson.

DR. ANDERSON: I'd say half a millimeter.

DR. ABRAMSON: Based on? This is knee and --

DR. ANDERSON: Well, I don't know. What's joint space like in the knee versus the hip?

PARTICIPANT: They're roughly similar.

DR. ABRAMSON: They're roughly similar. I mean, let me just ask Dr. Brandt, who's in the midst of an active study, to talk about the endpoints, radiographic there, and given the tools we have to work with, what do you think about this question, Ken?

DR. BRANDT: I don't think we can answer it. I don't think we can answer it today. Let it go at that. If we're looking at the effect of a drug, we can debate whether a difference between the placebo group and the active treatment group in slowing of progression of 30 percent, 50 percent, 70 percent, 10 percent would stand muster, but those are educated guesses.

In fact, we did that at the outset before we

undertook our study. I surveyed a number of rheumatologists internationally and posed that question, and it was between 30 and 50 percent the effect size that they would want to see before they considered that this was a useful drug, considering only structure in comparison with the rate of narrowing of the placebo group.

Those are educated guesses, and we have no idea how, if at all, they connect with anything that's clinically relevant.

DR. ABRAMSON: Dr. Dieppe?

DR. DIEPPE: I don't think we can answer it either, but I would just reinforce my belief that we cannot treat the knee and the hip as the same necessarily in this equation. I think Maxime's data on the hip is quite compelling, that if you have 50-percent loss, if you start with less than 50 percent in the first place, that's pretty good going, and it may be that the same's true of the medial tibial-femoral joint, but again even within the knee joint, we've got to specify what we're talking about here, which bit of it, but given the present discussions and the data I've seen, I'd go along with a 30- to 50-percent loss, rate of loss, change, if you start with a bad joint, but it may be very different if the joint's not very bad to start with, and then I think we know nothing and cannot assume anything.

DR. ABRAMSON: Yes, Ms. Malone?

MS. MALONE: I have a question. Just in the normal person, does the joint space differ between people or are they pretty much the same?

DR. DOUGADOS: There is one study coming from U.K., I think, 10 years ago, and in the 800 persons, and it was related to the age, the more you are, but it's only .05 millimeter difference. Otherwise, there is no difference between the right and the left, between -- and the woman has a lower joint-space width.

MS. MALONE: Well, is it significant enough so that it would make a difference in, you know, the number that we're looking for?

DR. DOUGADOS: I'm not sure that it will make a difference for what we are looking at. If I correctly understand your question, that was related to the normal joint-space widths, not the changes in osteoarthritis because usually there are two things we are discussing.

The first one is to conduct a study in order to prevent the occurrence of knee OA in patients. That is, we are dealing with normal knee joint-space widths, and the other possibility is to conduct trials in patients with osteoarthritis at baseline, and I do agree with Paul that the change of the joint-space width over time is probably completely different.

DR. ABRAMSON: Dr. Moreland?

DR. MORELAND: I have a question, I guess, for clarification from the agency. I'm not sure I consider OA a life-threatening disease, and are we really talking about developing the plan here for the approval of structure-modifying agents through the regular mechanism or through accelerated mechanisms, and my comment would be that I think in the current definition, I don't see where this should be something in an accelerated mode.

But I heard awhile ago that you consider RA as a life-threatening disease, but we're here to look at OA, and do you consider OA a life-threatening disease, and in your definition, are you really talking about an accelerated type of approach?

DR. JOHNSON: Yes. I think maybe Bill misspoke. I think you meant to say OA. It actually says life-threatening or serious, I think. Isn't that what the regs say?

DR. SCHWIETERMAN: Yes. I did say --

DR. JOHNSON: People can buy into the concept of --

DR. SCHWIETERMAN: -- it's a serious aspect of it, not life-threatening. The debilitation from OA as a serious entity is what we're talking about.

DR. ABRAMSON: Dr. Elashoff?

DR. ELASHOFF: In terms of the percentage figures that were being talked about, we need to keep in mind that it's really a short-term outcome that he was showing. It's replacement within three years, whereas if you're really talking about the whole history of the disease, it might be pretty important to talk about, say, within 10 years or other kinds of things like that.

DR. ABRAMSON: Dr. Witter?

DR. WITTER: One other regulatory point then, taking off a bit on Dr. Dieppe's comments and maybe kind of steering some of the discussion.

If we view, we meaning everyone, if we view hip and knee OA as being different entities and having a different natural history and responding differently to therapies, then should we as a regulatory agency be requiring for these kinds of products studies in both hips and knees as part of the registration, and in fact would the labeling say if it were to come to that, to be used for osteoarthritis of the knee or of the hip?

DR. ABRAMSON: Dr. Brandt, and then Dr. Dieppe.

DR. BRANDT: I think they do need to be split, but I think we need to be very cautious about using joint replacement as an outcome measure, and I think the PORT data for both hip OA and certainly knee OA from Indiana speak to that point, that it is not invariably so, that

only patients with devastating disease are operated on in this country. That's not true. Maybe it should be, but it isn't, and there are no standards for hip replacement or knee replacement. So it's an awfully soft outcome measure. It's important, but it's awfully soft as an outcome measure, and we talked earlier about the differences between community subjects and patients, not in the doxy cohort, which hasn't been followed long enough, but in other cohorts in Central Indiana of old people over the age of 65 with radiographic studies over a three-year period of time and serial WOMACs every six months, the presence of Grade 2 or Grade 3 OA had no impact on WOMAC scores which were pretty low and remained low, did not creep up with time and function scores as well.

So again speaking to the disconnect between radiographic change, and there was very little progression, at least in Kellgren and Lawrence grade, but the progression that did occur was not accompanied by changes in WOMAC pain or function scores.

DR. ABRAMSON: Dr. Dieppe?

DR. DIEPPE: I think the answer to Jim Witter's question is yes, you have to treat them as potentially different, and therefore you'd have to label separately. Of course, we don't know. One of the reasons we don't know the answer is we don't have a positive control.

One of the reasons we're in real trouble with this whole field, and we can't provide you any decent advice, is we don't have a positive control treatment to go with. The only thing that gets anywhere near it in my view is osteotomy, but the data on osteotomy is weak to get our understanding sufficient to provide you with the evidence.

I just want to add another complexity for you, just to make it more difficult potentially for you. I suspect -- and this actually relates to Ms. Malone's question, I think, or the discussion around it. It may be that we have to regard the genders as different as well. There is quite a lot of indirect evidence to suggest that osteoarthritis of both hip and knee can behave differently in the two genders as well as being different in themselves, and we have data to suggest that the determinants of pain and disability at the knee joints are quite different in men and women.

So I think we have to potentially think about that split as well as the joint split, which just makes life intensely more difficult for you and for us.

DR. ABRAMSON: Why don't we take one last -- I'm sorry.

DR. JOHNSON: Just one quick question for Paul. If you were going to use a 30 or 50 percent in bad knees, how would you define a bad knee?

DR. DIEPPE: 2.5 millimeters or less joint space at entry. That's a silly answer because it's off the cuff, but that's the ball park, I think.

DR. ABRAMSON: Okay. I think I'll take one more comment from Dr. Dougados and then ask the agency if there are other issues pertinent to this question that they would like us to flesh out before we move on.

DR. DOUGADOS: Just to go back to the comment from James Witter concerning the consequence of the labeling of the development of a compound in either hip or knee, I do agree with Paul that the issue is probably different, but I do agree with Jim when he said that the gender is important. The localization within the knee is important, medial versus lateral femoral. So a drug has to be developed in one specific localization, in one specific gender, and one specific age because age is also very important. Over 65, it's completely different than between 55 and 65.

So we have this kind of discussion within the Osteoarthritis Research Society group and also with the GREES move that was in the European Community to say, well, but in fact, to try to get a consensus, that is the reason for a meeting such as this one, and we have this discussion here in February '98, to say that finally we have to clearly differentiate and back and lower limbs, but perhaps

we don't have to go into the details of the lower limbs.

DR. ABRAMSON: Right. And now that we've clarified your Question Number 1, do you want us to further explore this issue with you?

DR. WITTER: I think we're heading in the right direction here. So a very helpful discussion.

DR. ABRAMSON: I guess the take-home is going to be data-driven, that the term "OA" is such a heterogeneous term between knee, hip, back, et cetera, that the data will drive the indication, I suspect, in many ways.

Okay. Number 2.

DR. LOVELL: Can I ask a very ignorant question? It seems that the clinical rate of progression -- and maybe comorbid factors could be different from hip and knee, but based on the animal experimentation, do you think the primary pathologic process at the level of the cartilage differs between the knee and the hip?

DR. ABRAMSON: I don't know that --

DR. LOVELL: And it will speak to a drug that has a uniform effect amongst all joints.

DR. ABRAMSON: I think the issue may not be -- and people may agree or disagree -- that the pathogenesis per se is all that much different, but perhaps the biomechanical forces, the local forces are such that if

you're trying to develop a drug based on rate of progression, that the rates of progression may be variable enough between the sites that you may not be able to use the data, at least that's one way of thinking about it.

DR. BRANDT: I'm not sure that the cartilage matters, and I think that's the thrust of the point that Jim Witter made in his first or second slide, that OA is increasingly viewed as a disease of an organ and not just of any tissue within that organ, like the cartilage, and it may be that sensory input proprioception or quadriceps weakness or bone stiffness, et cetera, et cetera, et cetera, et cetera, may be important determinants in whether those vary from joint to joint.

Biomechanical factors certainly do, and I think that it's better at this point in my opinion to be a splitter rather than a lumper.

DR. ABRAMSON: Dr. Hochberg?

DR. HOCHBERG: The other thing that supports splitting is if you look at large epidemiologic data sets, and you say that the validity of the radiographic feature for disease is its correlation with pain, that for the hip, it's different than the knee because for the hip, it's minimal joint space, less than 1.5 millimeters, is the most strongly and consistently associated radiographic feature with pain reporting. For the knee, it's the presence of an

osteophyte. So you know, we don't know.

DR. ABRAMSON: Go ahead, Dr. Harris.

DR. HARRIS: Can one at least say that we could look at the cartilage as perhaps a marker of some sort, though? I mean, that's an end result, and just in trying to get at some sort of measure by which one might make some sense of worsening, you know, you know, some measure, would cartilage then be seen as perhaps a measure, even if, you know, it itself may not be the critical factor in terms of osteoarthritis?

DR. ABRAMSON: I guess Dr. Altman raised the issue of arthroscopy as part of the endpoints. Is that what you mean by that, Dr. Harris, or what are you thinking?

DR. HARRIS: Yes. Well, what I mean by that is that, you know, I guess it's responding to the point where Ken said, well, look, cartilage itself may not be important. Certainly there are a number of factors that may contribute to this thing called osteoarthritis, but if one is going to measure the thing, you know, what in fact is the best measurement available, and I'm asking, you know, about the sense.

Is it cartilage? In which case, if it's cartilage, then thinning of cartilage would then be a surrogate mark in many respects here, but I can't see us