structure or mechanical load, and that also influences the synthesis of chondroitin. More load, more synthesis.

Other immune modulation effects for chondroitin in human, animal, and *in vitro* studies, downregulation of inducible nitric oxide antitoxin effects, and, again, some nonsteroidal type of anti-inflammatory effects, but not like nonsteroidal anti-inflammatory drugs.

Chondroitin and glucosamine are working on the cells to stop making these signals that maintain and exacerbate the catabolic cascade rather than actually knocking out a cytooxygenase enzyme, for example.

So I'd like to summarize as quickly as I can. I did want to mention that the oral bioavailability of each of these two ingredients has been well worked out. The chondroitin especially has been an issue because it's a macromolecule and, thus, how can it get in. Well, it does get in. A lot of fragments are absorbed into the bloodstream. A lot of them are partially

desulfated, and this is expected to account for some of its actions. Again, these are similar to what is seen by the chondrocytes. Since chondrocytes get plasma effusions, they see these fragments. And both glucosamine and chondroitin, after oral administration, have been shown to be incorporated into large macromolecular structures of cartilage in healthy animals, healthy humans, as well as osteoarthritic animals and osteoarthritic humans. That I think is important to show that the same processes occur in normal people and osteoarthritic people. Giving them glucosamine and chondroitin does get to the joints, and it does what chondrocytes and cartilage do, which is make matrix in both conditions. So that's why I think this continuum is just that, a continuum. And that is why I feel that normal people would be benefited from this.

The economic impact, as we have all seen the billions of dollars of cost and burden. In France, they've looked at 11,000 subjects using chondroitin, and because of their decreased NSAID

use and, thus, also feeling better and less other therapies, they actually came out, if not equal, ahead in the price game. So, in other words, for socialized medicine such as they have in France, this is a boon. They get to safely treat people, prevent long-term problems with the drugs and with the illness itself. That argues very strongly to me that you are reducing the risk, if not of the disease, then of the economic burden.

Now, there's also a similar study in Russia, but I haven't translated it yet, so I can't give any details. But their abstract reported that they did have more efficient economy of treatment of osteoarthritis.

So to kind of wrap this up, both glucosamine and chondroitin have been shown to prevent the loss of cartilage over time. Remember the turnover time of cartilage, one to three years. Look at the length of studies that have shown this, one to three years. Earlier stages of osteoarthritis showed larger effects at reducing the cartilage loss, indicating prevention of

progression over versus simply treating symptoms. And the effects were long-lasting after cessation. In other words, stop taking glucosamine or chondroitin, and the symptoms are--the reduction of symptoms and the improvement in the structure are maintained for months. This is not just a quick-time, rapid action type of nutrient. These are actually affecting the structural integrity.

There are the biomarkers that are affected. These biomarkers have been correlated with the signs and symptoms of joint degeneration and deterioration.

I'm going to skip over the animal and *in vitro* models. They do support the human clinical findings, but I would like to again reiterate that data from various types of publications for glucosamine and for chondroitin are very reproducible and very consistent for benefits that do support preventing joint degeneration. I feel the result is inescapable. There's not any other conclusion.

The time course of the findings in humans,

both symptomatic and structural, do fit the mechanisms of ingredients that work on the regulation of anabolic and catabolic properties.

We've seen how glucosamine can prevent progression of joint deterioration in human studies as well as chondroitin, and that's echoed by animal studies as well, which can be actually more controlled to answer the question than human studies can.

So glucosamine and chondroitin have the ability to prevent joint deterioration and joint degeneration by all the lines of evidence that are out there and, thus, reduce the risk of osteoarthritis, which has been defined as the progression of joint deterioration and degeneration to eburnation.

Thank you very much.

DR. MILLER: Thank you, Dr. Bucci.

Comments or questions? Dr. Archer?

DR. ARCHER: I'm trying to get clear. You've thrown a lot of information at us. But are you saying is joint degeneration a surrogate for

osteoarthritis or does it define osteoarthritis?

Dr. BUCCI: How about both? I mean, I hate to make it a bivalent answer, but how can you have osteoarthritis without joint degeneration or joint deterioration? The endpoint is eburnation and loss of cartilage, and joint degeneration and deterioration I think is loss of cartilage at one point or another. So I guess that's why I'm saying yes to both. Also, that's one of the characteristics of the radiological staging.

DR. MILLER: Dr. Krinsky?

DR. KRINSKY: Norman Krinsky. I would assume that in the normal joint, if one exists, the anabolic and catabolic processes are in equilibrium. And under those circumstances, if you treat that with glucosamine or glucosamine and chondroitin sulfate and you increase the anabolic processes and decrease the catabolic processes, does that, therefore, lead to an increase in cartilage? And what are the implications of that in a normal joint?

DR. BUCCI: Right, that's an excellent

question because I am--one of my answers is, Have you seen people with cartilage just pouring out of a joint? No. Even in acromegaly, which is really a regulatory problem with growth hormone, you do see extra cartilage, but not otherwise. And, in fact, if you give glucosamine and chondroitin into normal cultures, unless there's a need for synthesis, you don't make extra cartilage. You might synthesize a few more precursors, but they're not let outside the cell to make matrix. That's why I was trying to stress these are regulatory molecules. If you don't need them, they won't overdo it, so to speak. If you need them, they fit right in and help restore matrix.

DR. MILLER: Dr. McBride?

Dr. McBRIDE: You've mentioned that there's evidence that chondroitin sulfate and glucosamine are absorbed into joints. Is there evidence that they're absorbed into healthy joints, not inflamed joints?

DR. BUCCI: Yes. In fact, most of the evidence is in healthy animals and healthy humans

as well.

DR. McBRIDE: These are marker studies or--

DR. BUCCI: Yes, these are radiolabeled glucosamine, radiolabeled chondroitin. Labels on the sulfate for chondroitin and also the hydrogens on the sugar ring for both glucosamine and chondroitin; also tech-(?) 99 labeling of chondroitin as well.

DR. McBRIDE: Are there any comparison studies of absorption into inflamed joints or those that might truly have osteoarthritis and those that would be precursors, probably less inflamed?

DR. BUCCI: I know that there have been studies in osteoarthritic animals and even, I think, one or two in people that have looked at uptake into joints. I'm afraid I can't recall if there's any direct comparison.

DR. McBRIDE: But those would be osteoarthritic joints.

DR. BUCCI: Yes, so we do know that they can get into osteoarthritic joints and become

incorporated into macromolecules, also the same for healthy tissues.

Now, the rates of incorporation, I don't know if that has been quantified. If it I has, I just have not picked that up in the literature. There is obviously a lot here to remember. But I know that that has been looked at in animal studies, and the normal maintenance that is constantly ongoing is enough to label cartilage with glucosamine and chondroitin in a normal setting, if that helps answer your question..

DR. MILLER: Dr. Russell?

DR. RUSSELL: Yes, I was interested in the two studies that may have something to do with primary prevention of osteoarthritis. One was the finger osteoarthritis. You said that treatment prevented new finger osteoarthritis. Does that mean joints that were previously uninvolved that remain uninvolved? And presumably in the untreated group that there were some new finger lesions? And were those statistically significant differences or--I don't know the detail of the study.

DR. BUCCI: Okay. To clarify that, some of the studies did show a prevention of new lesions; in other words, no arthritic lesions in a finger joint, there was less appearance of new lesions in the chondroitin-treated group versus the placebo group. Some studies did not find it and others did. But pretty much all the studies did find that the prevention to the severe erosive stage from moderate-mild damage was prevented. I think that was near universal in each of those studies. And the effects were obviously larger and significant as time went on. Some studies did not see it at one year, but at two or three years they did see it.

DR. RUSSELL: And I wonder if you could clarify just a little bit on the knee study that you mentioned, that the non-osteoarthritic knees in this 2002 study were improved. Again, was this--not improved, but were not involved. Was this statistically significant from the non-treated group?

DR. BUCCI: I don't think that they looked

at this in a statistical manner because it wasn't one of the enterprises of measurement. I think it was an observation in the discussions. I think that my colleagues can speak to that, too.

DR. MILLER: Dr. Abramson?

DR. ABRAMSON: That was a very clear presentation, and I always need to have those fern-like molecules pointed out to me again. But I want to just discuss whether one can sometimes overly simplify very complicated tissue and talk about the chondrocyte as making and creating proteoglycans and collagen, because I think apropos the fact that this may be a different disease once established versus early on, these kinds of metabolic changes may be difficult to extrapolate over.

So, for example, if early OA, we know, is a proliferative hypertrophic disease where proteoglycan actually is increased in its production and not decreased, then it's not clear that in early disease, at least just playing the hypothetical here, that a decrease in proteoglycan synthesis should necessarily be corrected by the

addition of exogenous substrates like glucosamine. And then the changes occur, you know, through hypertrophy and the catabolic changes, and then you get this very complicated disease which is not just in and out of proteoglycan and collagen, but there's bone and there's synovial cells and there's interleukin-1. And at that point, the *in vitro* evidence I think is very intriguing that glucosamine and chondroitin, as you showed, can reverse some of these catabolic events. And that case is consistent with whatever kind of clinical evidence we may have that this is a beneficial treatment.

But I think going back on the table today of health claims, it's not clear that those effects, were they true *in vivo*, in patients, are necessarily applicable to these early changes. And I just--so that's a long statement. Do you want to comment on the actual complexity of this biology?

DR. BUCCI: Yes, I'd love to, and I'll try to keep it brief, obviously. But, no, that's a consideration I've thought about quite a bit,

obviously. Of course, there is a difference between osteoarthritis and just normal non-damaged tissue, and it does get more complex. But, again, the reason I made my whole presentation simplistic on purpose is because, no matter how complex it became, no matter what biomarkers you were looking at, no matter what pathways you were looking at, no matter what disease state, no matter what the state of cartilage was, whether it's in the increased production of proteoglycans in the early stages or the decreased production in later stages, they all go back to the same point, which is making more matrix. Sooner or later, everything points to that. It's almost a unified field area or unified matrix area, if I can coin a term, that regardless of which stage--normal, early, middle late osteoarthritis, damage with no signs and symptoms--sooner or later it's a problem with making the matrix. And glucosamine is intimately involved not only in making the matrix but in regulating it. And for whatever reason, the catabolic signals overwhelm the limited ability to increase the

anabolism. I think that the ability of chondrocytes to generate more matrix, they can only increase proteoglycan production from normal upkeep about 250 percent. I think that's from human and animal studies in general.

So, in other words, cartilage has a very slow, limited response to any of these complex stimuli. But that's the response to all of these.

DR. ABRAMSON: So I would just--I understand. I would just point out that there are two mechanisms of glucosamine and chondroitin that you're talking about. One is it's acting as a substrate to a building block for more proteoglycan. The other is a pharmacological action, which is somehow through receptors it inhibits the activation of chondrocytes in response to IL-1, and that probably is via a different mechanism, or one could possibly--that's two separate mechanisms: one is the available substrate, and the other is what it's doing to signaling that we really don't understand, except it does seem to do that, and what happens in

clearly established disease, and separating the relative importance of that I think is an interesting question that I think needs more understanding.

DR. BUCCI: I agree. But, conceptually, I would say that these are physiological roles and events, and these regulatory roles are trying to get tissue back to normal. That's obviously what our bodies try to do in every tissue. This is the way chondrocytes do it. They use glucosamine and chondroitin to try to return to normal, keep normalcy. If there is anything abnormal, then they are there to try to restore normality. And that really is what I think reducing risk and prevention of a disease is all about. How can you prevent disease if it's not there? Well, by these mechanisms you just described.

DR. MILLER: Dr. Felson?

DR. FELSON: I guess, once again, sort of a lovely, comprehensive discussion of many, many issues. Unfortunately, perhaps oversimplifying some difficult ones, which probably if there were a

variety of other osteoarthritis scientists in the room would take a week to discuss and not resolve.

One of them is I think you sort of presented the clinical data in a couple of ways that I think the rest of the audience sort of needs to comprehend a little bit, which is that my reading of the clinical data are not that convincing. And the reason for that is that there have been--all of the studies that you commented on, many of them--all of them, I think, the positive ones, are industry-supported. There have been three publicly supported trials of glucosamine, and all have been null, one of which is a very nice Canadian multi-center withdrawal trial. And that's one of the reasons why the NIH is now spending millions of our tax dollars on a trial to try to definitely determine whether glucosamine and chondroitin are efficacious. I think the jury is still out as far as treatment goes. I'm not sure how to interpret all the data that you described, and I don't disagree with you that the preponderance of it is supportive.

The other issue that you were--you used a phrase that I guess I would take issue with as a scientist thinking about these is cartilage loss. I mean, the clinical studies are not of cartilage loss. They're of joint space loss on the radiograph. And in all of the clinical trials that have been done, they're of joint space loss using a technique for radiography that most of us in the community find unacceptable as a measure of joint space loss and as a measure of cartilage loss. They're fully extended, weight-bearing films that we don't use in trials any longer because we have not been able to find them to be reproducible measures that one can follow over time to evaluate joint space loss.

Now, that begs the question of whether joint space loss over time consists of cartilage loss or, in the knee, meniscal loss, which it could and which MRI data are increasingly suggesting it likely does. So, you know, I think this is a very complicated set of issues, and I'm not sure in terms of treatment, much less prevention, what the

preponderance of evidence suggests.

DR. BUCCI: Well, I would like to comment on the North American studies on glucosamine. The letters and follow-up studies by those investigators admitted that they had walked into a veritable hornet's nest of placebo effects. They found that the public awareness and, thus, the subject's awareness was exceptionally high for the efficacy of glucosamine. And if they felt anything at all, they considered it due to glucosamine. In other words, they questioned the responders versus non-responders and whether they were in--it didn't matter which group they were in. The vast majority felt they were taking glucosamine.

Also, because of those expectations, if somebody didn't have a rapid enough effect for them, they had a no-sebo (?) effect. In other words, they figured, Ah, this isn't working, I should be free and clear of pain in two weeks. And when that didn't happen--as you see the time course is relatively long--that generated, as I said, a no-sebo effect. So they've racked up their lack of

statistical significance to the very large placebo response, in addition to--and that course makes the variability of the measurements quite wide and very difficult to find statistical significance.

If you look at the before and after values, they, of course, showed the same relative amounts of symptom reductions as other studies. And as to the--I also have read all the literature on the joint space narrowing versus cartilage loss, and regardless of how it wants to be labeled or named, these were double-blind studies, there was a control group, there was a difference. Something is happening. That can't be denied.

DR. FELSON: Just as a comment, you know, in the glucosamine randomized trials, the control group difference was generated in part by--what you were asked about earlier--an increased size of the active treatment group, which makes little sense in osteoarthritic patients followed longitudinally with better characteristics--with better methods of imaging radiographs. So with the fluoro or with fixed flexion views or with MRI in people with

established disease, there's not usually a pseudo-widening that occurs in large numbers. And that was what generated a lot of the positive effect that there was pseudo-widening and not narrowing.

DR. BUCCI: But that would also help reduce the risk of osteoarthritis, would it not?

DR. FELSON: If you believe the fact that pseudo-widening represents cartilage, it would. But the fact is that longitudinal studies of OA don't show in established disease that thickening occurs over time.

DR. MILLER: Dr. Mehendale?

DR. MEHENDALE: I have an issue with your statement earlier and assurance that cartilage maintenance, the processes involved in cartilage maintenance are very similar after the disease has occurred. I think some of the processes might be the same except that they have been enhanced now in disease. Some new processes may open up in disease in maintaining the cartilage. Certainly we have examples of such in other tissues. My own experience is in other tissues where injury has

occurred, and in restoring the structure and function of these tissues, new processes open up. And, therefore, equating the biochemical and repair processes that normally occur with those processes that occur in disease might be problematic.

I wonder if you have any comments on that.

DR. BUCCI: That's pretty much what I was trying to show here today, is that--are you speaking to me, sir, or--

DR. MEHENDALE: Yes.

DR. BUCCI: Okay, sorry. That's kind of what I was trying to get across here, is that the chondrocytes do the same thing to normally maintain their structure as well as to fight the insults and damage that lead to osteoarthritis and that lead to progression of osteoarthritis to eventual cartilage loss, and that imbalance is lost when there is osteoarthritis--or that balance is lost when there's osteoarthritis.

There may be differences in degree, yes, but that would be expected between a normal and a seriously compromised setting. But, nevertheless,

the basic mechanism is the same. Cartilage must be synthesized, and hyaluronan and synovial fluid also.

DR. MEHENDALE: Well, I feel that it is not the same. I think the new processes open up once the disease occurs in contrast to the normal processes before the disease occurs. And that's the point I was trying to make. And it has implications, one that was already discussed, and that is possible enlargement or increase in size of the tissue when you supplement with precursors in large doses in a normal situation.

So equating those and saying with a broad stroke of the brush that the processes are the same in normal as well as in disease processes creates problems in my thinking. And I think for an individual who takes these supplements also could be problematic because the process may not be the same in normal versus disease conditions, and that's the point I was trying to make and attract your comments, Dr. Bucci, on this line.

DR. BUCCI: I think my answer would be

let's start off with normal cartilage. If you feed it glucosamine and chondroitin, not much difference--nothing will be really different. They'll stay normal. They won't be overgrown. The synthesis won't necessarily be stimulated. However, if any of these events happen that are associated with osteoarthritis, then the glucosamine and chondroitin that are there start to do their actions that have been shown in osteoarthritis studies. So, in other words, if it's working in osteoarthritis, it will work whenever those same events are occurring even before a diagnosis has been made.

DR. MILLER: Dr. Lane?

DR. LANE: I want to take that one step further, and I may need Dr. Abramson's help here. But it's my understanding that prior to the joint becoming painful, there are biochemical changes that occur in cartilage metabolism, and one of the big ones is actually the proteoglycan that's made is actually much smaller, monomers. They're not normal. And those could appear to look like they

increase the joint space, but they're not going to work as well. And they don't work as well.

So one of the questions I have to you is: Do you have data that shows that when the glucosamine and chondroitin is put into the joint and OA chondrocytes that the proteoglycans are the normal ones? Isn't that more what you were trying to get, Dr. Mehendale?

DR. BUCCI: I think some animal studies speak to that. I don't know if they've actually sized the proteoglycan aggrecan molecular weights or the chain links of chondroitin sulfate itself. But the fact that if you have chondroitin or glucosamine available when these differences in proteoglycan synthesis are occurring, you do prevent the progression of osteoarthritis. That has to account for, I think, an ameliorative effect.

DR. LANE: Well, I don't know. Our measurements, as Dr. Felson said, are not sensitive enough at this time that we could even--I don't know if we can say that. But are the proteoglycans

generated normal or ones seen in disease?

DR. BUCCI: Okay. I can't answer that right here and now, so you have to figure that out for yourself. But I think that the animal studies show that a lack of lesions indicates that they are more towards normal than not. Otherwise, you would be seeing some of the earlier stages of osteoarthritis and you would not see the protection that's been shown in the studies.

DR. LANE: Okay. One other point. You mentioned inhibition of cartilage breakdown under chondroitin and then decrease in biomarkers of cartilage loss. You happened to mention one that comes out of the bone, the deoxypyridino-line/creatine ratio. I think you mean creatinine but that's okay. That tends to be a bone-collagen cross-link that mostly comes from bone. Are you making a statement that there's a hard tissue effect of chondroitin also?

DR. BUCCI: Correct. That is a good marker of bone turnover. There is obviously subchondral sclerosis associated with

osteoarthritis. There have been some X-ray findings of reduced sclerosis in some of their earlier glucosamine studies, so that would synchronize with the findings of the decreased deoxypyridinoline--I can never say that--creatinine ratio. So, yes, obviously there is some sort of bone involvement.

Also, bone is calcified cartilage, is one simplistic viewpoint, and any remodeling of bone must, again, start with synthesis of the matrix, the organic matrix, which, again, is most chondroitin sulfate and Type I and III collagen. So I didn't want to get into the roles of glucosamine and chondroitin in bone because it's less extensively studied, but, again, it is the precursor for the beginning stages of bone turnover maintenance. So that would definitely be expected in osteoarthritis.

DR. MILLER: Dr. Harris?

DR. HARRIS: Yes, Dr. Bucci, I gathered from your presentation that in order to realize the full effects, the full benefits, both chondroitin

sulfate and glucosamine are required. Yet the evidence that you're citing is showing studies that are using these compounds individually. And my question to you is: Are you aware of any studies that may have tested them individually and compared chondroitin sulfate with glucosamine administered simultaneously, possibly seeing synergistic effects? Could you comment on that?

DR. BUCCI: Yes. Well, we're saying that glucosamine alone can reduce the risk of osteoarthritis and chondroitin alone can reduce the risk of osteoarthritis, and, therefore, glucosamine and chondroitin. So we don't necessarily say you have to combine them, although that is what has turned out to be the most popular dietary supplement for consumers.

There are no human studies at this time of the head-to-head comparison of glucosamine versus chondroitin. I take that--

DR. HARRIS: Are we led then to believe that we have an over--

DR. BUCCI: I take that back, sorry.

There was one where they injected Arteparon, which is a polysulfate of chondroitin, versus glucosamine, and actually the results had some minor differences, but both were successful compared to a placebo.

Now, Arteparon is a different entity than chondroitin, and I have not used that data in my presentation simply because it is hypersulfate and, thus, has some anticoagulant properties that chondroitin does not have. So we have some indication that they are roughly equivalent in humans.

I think there was another early study comparing injectable glucosamine, iodine and glucosamine sulfate, versus oral chondroitin sulfate, and I think the investigators said that chondroitin sulfate actually had better clinical effects. But that was not a blind study, so I really hesitate to use that as an example.

There have been animal and *in vitro* studies done by Lippiello and associates answering this time of question, and they have found a larger

effect on whatever they were looking at in terms of reducing the incidence of osteoarthritis induced in animals or in proteoglycan synthesis in cartilage cultures with the combination over that of each individual. Each individual was significantly different or had more benefit, but combined, there was, again, an additional benefit. So, so far, it's just in the animal and *in vitro* stages for a synergistic action.

DR. MILLER: Dr. Espinoza?

DR. ESPINOZA: My question was already answered. Thank you.

DR. MILLER: Dr. Nelson?

[No response.]

DR. MILLER: Dr. Abramson?

DR. ABRAMSON: Whether the health claim of prevention or--I mean, that's going to be a clinical evidence judgment at the end of the day, in my mind. But just how the science informs our thinking about that, I just want to get a clarification because I don't agree that a chondrocyte in normal is the same as a chondrocyte

in disease, which seems to be, I think, where you were going with this. I think a normal chondrocyte and an early OA chondrocyte are different, and an early OA chondrocyte is different from an established OA chondrocyte. We each do different things, so in our lab we study gene expression, and I can tell you there's 300 different genes in the hypertrophic chondrocyte from normal and there's 300 additional genes when they're diseased. And understanding OA is understanding those differences. And that's not even counting the gene products that are coming from surrounding cells.

So whatever effects physiologically or pharmacologically glucosamine may have, I think you have to look at each stage from normal to hypertrophic to established disease independently. That doesn't address the question whether it's preventative or not. It's just, I think, for the purpose of this session, the science has to be thought about in those kinds of ways, I think.

DR. BUCCI: I agree. You're right. I'm not saying that the chondrocytes in normal and

osteoarthritic cartilage are the same. They're obviously different. That's evident.

What I'm trying to say is that the response of the chondrocyte to insults is production of matrix, and that's a similarity between normal and disease. It is, bottom line, the same end result, trying to repair the matrix. That's the similarity I'm trying to get across, so I hope that clarifies it.

DR. MILLER: Dr. Cush?

DR. CUSH: I want to ask you about the surrogate that we're talking about here, that being cartilage degeneration. I think most of us in rheumatology would actually consider cartilage degeneration the definition of osteoarthritis at its earliest and also at its latest stages and that there is a continuum there.

So I'm not sure it's an adequate surrogate for the healthy population and, therefore, the administration of health claims products. Moreover, I don't know that you've connected the dots here, meaning that giving glucosamine and

chondroitin sulfate leads to improvement in a surrogate measure which is reasonable and widely available and then that prevents disease. I mean, I think you've shown lots of disparate data, trying to combine human and animals, and we have to make leaps of faith. But, again, I don't know that there's a good connect-the-dots or succession in well-done studies to allow for that "if this, then that" sort of statement.

So, A, I'd like you to comment on the use of the surrogate here of cartilage degeneration and, B, do you think there is enough evidence that you can make the claim that taking the oral supplement will then lead to improved disease? Again, I'm not sure that that's been proven.

DR. BUCCI: I think what you're referring to as not proven is that we don't have the kind of epidemiological observational data as, say, calcium prevents and also treats osteoporosis. There are many similarities and parallels there, and the epidemiological evidence of feeding glucosamine to humans, a human population, and then looking for

onset or incidence of diagnosed osteoarthritis is not there. That is the reason we're all here trying to figure out if these so-called treatment studies do affect the process. And if I may borrow the analogy of calcium to osteoporosis, it does slow and prevent bone loss once it's already occurring, as well as preventing it when it is already normal and not in a state of loss. So you don't have that missing piece to the puzzle in the chondroitin in terms of populations.

Obviously, those are extremely long-term studies that, even if started tomorrow, would take probably longer than any of us would benefit from the results to conclude. So, therefore, that's what I'm trying to show you is that we have this piece of the evidence. And if you as a committee feel that that's enough that it should reduce the risk or it reduces the risk to joint degeneration, then that's what we're here to decide.

I think the evidence I've shown is very credible. It's very reproducible and very consistent. It fits with the known roles of

glucosamine, the known roles of chondroitin, and the known roles of cartilage during aging and health. So I think the chondrocytes know what they're doing ultimately.

DR. MILLER: Dr. Lund?

DR. LUND: In Slide 25, you cite the evidence for the effect of glucosamine and, in Slide 31, the evidence for the effect of chondroitin sulfate. I wondered, in looking at those studies, as you have already addressed in the Canadian study, are there some mitigating factors or are there factors in any of those studies that would link together to suggest why there are some studies that suggest that there is not a supportive role for either of those compounds?

DR. BUCCI: Yes, other than the placebo effects and the wide variability of measurements that I've already alluded to, there are some other reasons. Some of these studies that I listed as non-supportive were of relatively short duration or used an ineffective or a low dose. In fact, for chondroitin sulfate, they have done studies at

different doses showing that doses above 400--starting at 800, actually, are significantly different from placebo and doses below aren't for long-term effects.

I think some of the other non-supportive studies--if I can remember which ones they are. Usually it was the short duration and the wide--almost always a wide variability in the measurements. And it was that variability that precluded statistical significance. Although if you look at the before and after values, they were of the same--the mean was of the same magnitude as in the studies that did show significance. So it was really statistical power issues with many of those studies.

As I was pointing out, most of the large human clinical studies, it was overwhelmingly in favor of supportive evidence, finding a significant benefit. For chondroitin there were no non-supportive studies.

DR. MILLER: Thank you all very much. Thank you, Dr. Bucci.

DR. BUCCI: Thank you.

DR. MILLER: I think it's time we took a break. Please be back in 15 minutes. That's 10 minutes of 11:00.

[Recess.]

DR. MILLER: Can we continue? The next speaker is Dr. Lucio Rovati and Dr. Roy Altman from Rotta Pharmaceuticals.

DR. ROVATI: Thank you, Dr. Miller, members of the Advisory Committee, members of the FDA. My name is Lucio Rovati, and I'm Executive Medical Director of Rotta Research Laboratorium, which is the headquarters and research center of the Rotta Pharm Group that includes among the subsidiaries Rotta Pharmaceuticals in the United States. And I will give some brief introductory remarks. I will then talk about the clinical evidence supporting the health claim and the petition that we made. And then I will give the microphone to Professor Roy Altman from UCLA, and he will be supporting me with some animal and mechanism-of-action data. And I will be closing

then with some closing remarks.

This is the title of our petition, and thank you very much for giving to us the opportunity of presenting to you today some of the data that, in our opinion, support this petition. This is the actual accepted title, "Crystalline Glucosamine Sulfate Reduces the Risk of Osteoarthritis." The original title was "...Reduces the Risk of Osteoarthritis, Joint Structure Deterioration, and Related Joint Pain, and Limitation of Function." But after the remarks the FDA made, we agreed to truncate the claim because, actually, we believe that there are enough data to support the claim for reduction of the risk of osteoarthritis. And we will concentrate only on crystalline glucosamine sulfate, which is in the USP called glucosamine sulfate sodium chloride, because this is the compound we've been studying and this is the compound on which has been produced the largest amount at least of clinical data.

Just to give you a brief background, glucosamine sulfate, as we intend it in nature, is

highly agroscopic and cannot be used in any pharmaceutical preparation. You have to stabilize glucosamine sulfate, and we did it with crystalline glucosamine sulfate, which is the stabilized form of the glucosamine sulfate salt that contains as a stabilizer sodium chloride and, again, is in conformity with what is described in the USP 2004.

When we talk about glucosamine, we are talking about different substances. This is glucosamine as a certain chemical formula, as a certain molecular weight, and when we are talking about glucosamine hydrochloride, we're talking about a particular or peculiar salt of glucosamine, the same for glucosamine sulfate. I will refer to crystalline glucosamine sulfate, which, again, is a different substance than the others in that it's a stabilized form of the glucosamine sulfate salt, which is a different salt than the hydrochloride. Whether all of these are equal or not, we do not know, but the only evidence, at least the clinical evidence available is with this substance.

Let me enter in my real presentation,

which is the clinical trial evidence supporting the claim that we made for crystalline glucosamine sulfate.

Well, there are at least three good--excellent, I would say, high-quality systematic reviews and meta-analysis of randomized controlled clinical trials with glucosamine sulfate supporting at least its effect on the symptoms of osteoarthritis in patients diagnosed as such. The first one was published by Dr. David Felson's group in the JAMA in the year 2000 prior to the most recent advances in this field. The second one is the Cochrane Review published early in 2001 that, again, could not take into account all the new studies. And only the last one, published last summer by Richy in the Archives of Internal Medicine, could take into account all of the studies that have been published so far.

All meta-analysis, as I was mentioning, documented the efficacy and safety at least on the symptoms of osteoarthritis. Our crystalline glucosamine sulfate was used in 86 percent of the

trials. There are very few trials that could be examined with other glucosamine preparations that, according to the author, gave less favorable results. And, again, only the third one could consider two new long-term trials of crystalline glucosamine sulfate on which I will focus your attention today.

This is just to remind you, the first trial was published in the Lancet, early 2001, by the group of Jean-Yves Reginster, and the second one in the Archives of Internal Medicine late in 2002 by the group of Karel Pavelka in the Czech Republic. So both are European clinical trials.

There were two prospective randomized, placebo-controlled, double-blind, parallel group trials of three-year duration. Patients were actually diagnosed with knee osteoarthritis, according to the American College of Rheumatology criteria, and they were studies of reasonable size. The sample size was calculated and actually turned out to be a good sample size. There were around 200 patients in each of the two studies.

Treatment with the standard formulation, once a day, glucosamine sulfate, when I say the dose I always refer to glucosamine sulfate, 1.5 grams once daily continuously, which means every day for three years, or the corresponding placebo. And very quickly the results--I will show them very quickly, but the rheumatologists here know that this was the first clinically tested agent that was able possibly to prevent the progression of osteoarthritis joint structure deterioration as determined by radiographic joint space narrowing. We may come back during the discussion on the issue raised previously by Dr. David Felson. Clearly, this was the standardized methodology adopted and the only one available at the time of the trial. It's clearly not the methodology that we will use today, but we've also published validation data that this methodology was not biased by any confounder with respect to the results. And the compound was also able during the three years to reduce the functional impairment or prevent the progression of function impairment and pain by the

validated indices that we today use in osteoarthritis research.

Joint deterioration, in our opinion, is an actual indicator, predictor of osteoarthritis, and this is fundamental for (?) diagnosis, and it is invariably present in all patients with definite OA. Cartilage deterioration is the most widely accepted surrogate endpoint of joint degeneration, perhaps not the best, but it's the best that we have today. It can be indirectly assessed by plane radiography measuring changes in joint space width. Again, joint space width, radiographic joint space width, may not be the best in absolute terms, but it's the best that we have available today, and indeed, the measurement of joint space width is accepted by all scientific and regulatory guidelines, including the draft by the FDA and the final version of the European agency, to assess the progression of osteoarthritis. It is valid. It's an accurate measure of cartilage thickness for credible studies. It's reliable. It has good precision of repeated measurements, and it is

sensitive. And several epidemiological studies have shown that the natural history of knee osteoarthritis, for example, is a loss of around 0.1 millimeters per year in the different stages of the disease.

Of course, I will not go through all the slides that we have prepared, but we have provided you with a copy of everything, so also the ones that I will skip.

This is just to remind you the results of the Reginster study published in the Lancet. According to what we saw on the mean or minimum joint space width, it was actually around 0.1 millimeter per year loss of joint space that did not occur, was prevented with glucosamine sulfate, and the results are significant. And the same is true for the Pavelka studies. We had X-rays at every year, and at every year there was a progressive joint space narrowing in the placebo group, more or less of the same size as in the Reginster study; no progression with glucosamine sulfate; and, again, the difference was

statistically significant.

The results, as you've seen, are very consistent. This is the meta-analysis published by Richy last year, and you see that the results of the two studies are very consistent and, of course, show a difference versus placebo.

Just to show you that we were not probably affecting only cartilage or what we can measure with joint space width that I believe is cartilage, although it's possible that it may be confounded by something else, we were also measuring some of the other joint deterioration aspects that we can measure radiologically. For example, in the paper of Pavelka, we described how the glucosamine sulfate was able to prevent the increase in the proportion of patients worsening the osteophyte's core at the endpoint. You see that there were 20 percent with placebo versus 6 percent in the active group. So we were preventing also the bone reaction, the subchondral bone reaction. At least this is what it seems from this data.

Concomitantly to that, we had a decrease

in symptoms that was significantly better with glucosamine. This is the pain sub-scale of the WOMAC and the Reginster study. This is the function sub-scale in the Reginster study, again, of the WOMAC, and the same results for Pavelka. Total WOMAC, this is glucosamine, this is placebo; WOMAC pain, again, a reduction, always significant; WOMAC function, and WOMAC stiffness.

Now, I think that these studies are well described in the literature, are known from our petition, and everybody perhaps is familiar with this. The real crucial point is why do these therapeutic trials of knee osteoarthritis with crystalline glucosamine sulfate may support the claim for disease prevention. And we've listed here some of the points that I will touch on in the rest of my discussion and in the discussion of Professor Altman, and including the mild to moderate characteristics of the patient population, the data obtained on the contralateral knee in these patients, the structure-modifying effects in patients with milder characteristics at entry. The

disease outcomes in longer-term follow-up--these are new data--are not included in the petition because they were presented, not yet published in full but presented after the petition was submitted. And then Professor Altman will expand a bit on the facts of the compounding prophylactic animal models and the mechanism of action supporting the short- and long-term effects on symptoms and prevention of joint structure changes.

Mild to moderate characteristics of the patient population, I want to remind you again from this slide that it's taken, it's derived from the two publications of Reginster and Pavelka, and I want to draw your attention on this. Most of the patients, over 50 percent in the Pavelka trial and over 70 percent in the Reginster trial, had Grade 2 osteoarthritis according to Kellgren and Lawrence. And as the experts know, Kellgren and Lawrence Grade 2 is usually recognized as mild osteoarthritis. Even the joint space narrowing in Grade 2 osteoarthritis is affected to a lesser extent than in more serious or severe grades. So

most of these patients had actually mild osteoarthritis, perhaps some of them also with still a rather intact joint space that was our primary endpoint for the structure modification.

Actually, if you look at the joint space width at the minimum distance in the joint, you see that both in the Reginster and Pavelka studies, in the two groups the average was around four millimeters. It's clearly not severe osteoarthritis, but it's very mild. And if you go then on the mean joint space width in the study of Reginster, you see that it's over five millimeters. So it's not far from what is normally found in a normal population. And, also, the symptoms of the disease were rather mild to moderate.

So the first conclusion is that patients in the two long-term trials had mild to moderate symptoms at enrollment, and especially they predominantly had mild joint structure changes. And the effects observed in this population may, therefore, be transferred--with some caution, of course, but may be transferred to the general

population at risk for osteoarthritis.

The second topic I want to focus on is the data on the contralateral knee, and these are also published data from the Lancet paper and from the Archives paper. You see, this is the mean joint space width in the Reginster cohort in the contralateral knee of the patients, and you see that this joint space width is pretty large. I think it's very difficult to differentiate this joint space in the contralateral knee from that of normal patients, of a normal, healthy individual. But, actually, you see that we were able--well, the joint space narrowing was present also with placebo also in the contralateral knee and did not occur or occurred to a lesser extent in the glucosamine sulfate group, and the difference in this particular study is statistically significant.

The same trend was evident in the Pavelka study. You see, this is the minimum joint space width, almost five millimeters. It's really hard, in my opinion, to discriminate this from normal joint space width, and we see the same trend as

before, a loss under placebo, a lower degree of loss or no significant loss with glucosamine. The difference here is not statistically significant, but the trend is the same as in the Reginster study in the contralateral knee.

So, again, a small conclusion on that. The contralateral knees of patients in the two long-term studies had baseline joint space width values that are hard, in our opinion, to differentiate from those of the general population. Nevertheless, the trend for the prevention of joint space narrowing was similar to that observed in the signal joint that was the real primary endpoint of the study.

Structure-modifying effects--and, to some extent, symptoms, but I will not show that--in patients with mild characteristics at study entry, we published a couple of papers on that. This was a sub-analysis we published early last year on osteoarthritis and cartilage. It's a quartile analysis of baseline mean joint space width. And when we took the patients in the quartile with the

highest or better preserved joint space at enrollment, these were actually the patients that were suffering a joint space narrowing under placebo and in which the effect of the compound was evident in preventing the joint space narrowing.

Conversely, in the more severe patients, those in the lowest quartile, there was no apparent progression, at least in this particular condition of the study, and, of course, you do not see much with the compound because they did not progress very much.

So, again, a short conclusion. The structure-modifying effect of crystalline glucosamine sulfate was particularly evident in those patients with better preserved joint space at baseline, whose joint structure is closer to that of the general population. Conversely, the symptom-modifying effect that I did not show, but it's published in the Scandinavian Journal of Rheumatology, is present irrespective of baseline joint structure conditions, which, in my opinion, confirm both the previous data on treatment of

established osteoarthritis and underlines the potential for prevention.

These are the outcomes in longer-term follow-up. This is, in my opinion, very important. These are new data, have not been published in full yet. There is an abstract that has been published and presented last year at the American College of Rheumatology, and in which we've gone to see what happened to the cohort of these patients years after they stopped the trial with respect to the hard clinical outcomes of the disease. When we talk about a complex issue like osteoarthritis, which sometimes is difficult to diagnose, it's difficult to relate the joint structure changes with the symptom changes, we may have difficulties in saying exactly who is osteoarthritic and who is not. So perhaps in order to be on the safe side, we should go to see the clinical endpoint, like myocardial infarction, for example, in another completely different disease. So we went to look at what happened to these patients with respect, for example, to disability and especially joint

surgery in the long run.

So in the trial of Jean-Yves Reginster, we wanted to perform a follow-up evaluation in patients that were previously in the trial to evaluate the occurrence of osteoarthritis-related joint surgery during the follow-up after the trial and after they stopped the medication, and also we assessed several secondary endpoints.

We could retrieve 83 percent of the original sample, which is good, because this was five years after the end of the study. So, overall, there is on average an eight-year observation period--three years of the trial on average, and five years of follow-up after drug discontinuation.

Patients after the trial had received standard of care. Glucosamine sulfate is not available in Belgium as a drug, and, therefore, these patients were relatively clean from this point of view. And these are the results. Actually, there were more patients undergoing knee or hip surgery in the former placebo group compared

to the glucosamine sulfate former group. And there was a reduction or a trend for a reduction of risk of 48 percent, which is not statistically significant but it is at the very limit of statistical significance, and to me it's very important given the sample size.

When we go to look for a number of knee or hip surgeries considering multiple events, the difference is similar and is really very close, if not statistically significant, and the same for the number of knee surgeries only.

It's important that you note that actually we included the hard outcomes of the disease, total knee or hip replacement, but also we included some patients who underwent other surgeries, such as joint debridement and meniscectomy--meniscectomy, of course, for degenerative meniscal disease. So it's clear that when we go to see the number of knee or hip replacement, we have exactly the same trend. It's a 44-percent decrease in risk, but this becomes less closer to significance. But I have some new data on that that I will show you.

This is important because in the two studies we've shown that we were able to prevent the number--to reduce the proportion of patients that had severe joint space narrowing. You see that there were 30 percent under placebo in the first study versus 15 percent with glucosamine sulfate, and in the second study a similar trend, 14 percent versus 5 percent, with a reasonably small number needed to treat to avoid such a worsening.

Well, we went to see what happened to these patients during the follow-up, and, actually, these patients with severe joint space narrowing had a higher chance of undergoing knee surgery during the follow-up. There was a three-fold increase in risk. So we've shown that by preventing this severe joint space narrowing, we may be preventing later on the consequences of the real clinical outcome of the disease, as we've actually indicated in our analysis.

So it's important what we did during the trial, but if we go to look to the overall eight-

year period, we can see that actually placebo over the eight years has lost a considerable amount of joint space compared to glucosamine sulfate, the formal glucosamine sulfate group, and the difference was statistically significant.

In summary, three-year treatment with crystalline glucosamine sulfate prevented osteoarthritis-related lower limb surgery, which is a clinically relevant disease outcome, during an average for the follow-up of five years. And this may be due to the structure-modifying activity achieved during the treatment and an overall delay in joint structure changes, which to me speaks very much in favor of prevention. I didn't show the data, but, in addition, the patients previously on glucosamine sulfate had a long-lasting symptomatic effect, better quality of life, and a lower utilization of health resources during the last year of the follow-up.

I would like to introduce now the talk of Professor Altman about the effects in prophylactic animal models of the disease that may support a

preventive role for the substance and on the mechanism of action. Again, I would like to make clear that these alone are not to me essential to support any claim, but they are important in that they support the clinical data that we have shown.

DR. ALTMAN: A little over ten years ago, Dr. Lequesne indicated that in structure-modifying trials, in order to develop at the time we called it chondro-protective agent, that you should really have at least two different animal models to support at least the idea. And so I'm going to give you that.

First, I'd like to just show you the structure of glucosamine. It hasn't been shown so far. This is glucosamine sulfate, obviously, and the sodium salt. It does hydrolyze in the stomach, but a fair amount of it is absorbed as a sulfate, and the sulfate is absorbed separately. I'm going to actually address that.

This is just a list of some of the trials that have been performed on animal models. I'm going to only emphasize the last two, and the first

of those Jean-Pierre Pelletier's study from Montreal.

This is a canine model of osteoarthritis. What you do is you transect the anterior cruciate ligament. It destabilizes the hind limb of the dog, and over a period of weeks, they develop osteoarthritis that becomes fairly stable at about 14 weeks, but up until 14 weeks has progressive changes. In this particular study, they examined the tissues at eight weeks. They used three different doses of glucosamine and, of course, a control group.

Just to give you an idea, I'm sure you'll hear more about this later from Dr. Witter, but in this particular model you can see the ulcer on the condyle of the animal to show you how they develop over a period of eight weeks.

Now, I want to point out that both of these studies are prophylactic studies. In the past, I've done many therapeutic studies where you allow the arthritis to develop over a period of weeks and then you start to treat. In both of

these studies that I'm talking about, the treatment was started immediately after surgery. So we're getting at the onset of the illness.

The second slide from Dr. Pelletier's group shows the osteophytes that occur along the joint margin that are similar to human osteoarthritis. Now, the canine model is actually a very good model for human disease. Of course, there's nothing that really is completely the same as human disease. The rabbit model that I did is a little bit less specific.

This shows you the femoral condyles of the osteoarthritic and the treated animals, showing you the ulcers up above that were not as great as, certainly lesser size in both the condyles and the tibial plateaus of these dogs.

And the histology. The question was asked earlier: How do you know whether the proteoglycans are of proper size? That can be done, and we used to do that. We now just look at safranin-O staining. Safranin-O stains the proteoglycan molecule, the aggregate proteoglycan molecule, and

you see there's a loss of safranin-O staining in the osteoarthritic model. There's a fast green counter-stain to point up the rest of the tissue. The other things that are looked for is surface disruption. You can see significant surface disruption here, a lesser degree here. Cellularity is actually decreased in part of the tissue here, the cellularities here. This doesn't show the tide mark, and I'll show that in the rabbit model.

In any case, Dr. Pelletier also looked at--Drs. Pelletier, I guess I should say, also looked at the amount of stromelysin that was present, and the amount of metalloproteinase that was present in both, in the membrane was actually decreased where the amount of amount of metalloproteinase in the cartilage was not significantly changed, actually. And this is consistent with some of the others that's been presented.

Because of time constraints, I'm going to quickly go into the study that I performed, and this is a lapine model, a rabbit model, where we had four different groups--two different dosing

groups, and, of course, a placebo osteoarthritic group and a placebo normal group.

We have done other studies with glucosamine looking at it in normal cartilage, and it does not seem to change the structure of normal cartilage, at least in the animal model.

Now, the difference in the gross anatomy here is that we used what's called a Meecham stain, which is just india ink that's applied to the surface of the cartilage and then wiped off so that you can get a decent picture. And you can see the normal doesn't retain any india ink; the osteoarthritic contains considerable india ink, showing a lot of the surface disruption. And you can see in both the low-dose and the high-dose glucosamine-treated animals that they had very little in the way of retention of the india ink.

Histologically, it supports the same thing here. The safranin-O is much more intense in stain. You can see the tide marks intact here. The tide mark is disrupted here. It's more normal in both the low- and high-treated group that retain

the safranin-O, retain the surface, and so on this model the glucosamine was actually preventive of disease.

Now, I did want to go over just a couple of things on mechanisms of action. For instance, there's a considerable amount of data showing that there are anabolic effects in the cartilage for proteoglycans and some of the minor sugars, such as perlecan, in cartilage.

Secondly, there is an anti-catabolic studies showing there's a decreased amount of actual functional stromelysin in the tissue as well as that the glucosamine decreases the aggrecanase, and this is by John Sandy, one of the most critical people that I've encountered in my editorial work.

One of the things here--this is a culture medium; this is where you take interleukin-1 and put it into cultured chondrocytes. Osteoarthritis is very much an interleukin-1--could be arguably an interleukin-1-driven disease. Even though TNF is there, it's much more dependent on interleukin-1. And in this particular study, you can see that the

amount of proteoglycan is retained with increasing doses of glucosamine and the amount of proteoglycan that seeps out into the culture medium decreases with increasing doses.

Now we're going to get into the concept of inflammation. The term is "osteoarthritis," and Dr. Abramson and Dr. Pelletier have published a very nice editorial in Arthritis and Rheumatism pointing out that osteoarthritis is really an inflammatory disease. And this is some of the evidence for it, that interleukin-1 does induce prostaglandins and nitric oxide release from chondrocytes. Prostaglandins are, of course, the inflammatory mediators. Nitric oxide may have something to do with the ability of the chondrocyte to survive. It may stimulate programmed cell death.

In both of these, you see a reduction with the glucosamine and a dose/response relationship, and these are doses, by the way, that are achievable with the oral 1500 milligrams.

Going a little but upstream from the

prostaglandins to the enzyme that actually produces the prostaglandins, IL-1-induced COX-2, cyclo-oxygenase 2, as well as inducible nitric oxide synthetase, are reduced--are increased with osteoarthritis and their expression is actually decreased with the amount of--with administration of glucosamine.

Did I skip one there? No.

Now we're moving further upstream, and here we see that interleukin-1 reduces NF-kappa B activation. And this is important because now we're starting to get into the idea that we're moving upstream in the cell and where the glucosamine may be actually having its function. And in this particular study, you can see that the amount of interleukin-1-stimulated cartilage degradation is reduced with the glucosamine. And that can be demonstrated very nicely with some staining that you can see here with the basal cell amount of NF-kappa B, the stimulation with IL-1 beta, and the suppression that you can get with the glucosamine, no effect with glucosamine alone, and

partial suppression with the IL-1 beta plus the glucosamine.

That was from one study. This is from a different study indicating that COX-2 messenger is actually reduced in chondrocytes that are stimulated with interleukin-1 beta, again pointing out reduction in the inflammatory mediators.

So what we've come to is a hypothesis that the interleukin-1 phenomenon that goes through a second messenger to stimulate the chromosome to produce the prostaglandins is blocked by nonsteroidal anti-inflammatory drugs, but this part doesn't seem to be. Whereas, if we go to glucosamine and paralyze the NF-kappa B, at least the 50 molecular weight product at this level, then we interfere with the production of the prostaglandins as well as the MMPs, et cetera.

There's just one last thing I wanted to point out, and that is the question as to whether the glucosamine hydrochloride or the glucosamine sulfate makes a difference. There's really not a lot of information on this sulfate, but there's two

studies that have come out fairly recently that have indicated that the amount of serum sulfate is actually increased when you use glucosamine sulfate. And here's one of those studies, the first of them, and this is the second of them, indicating that--this is from Marcel Nimni's group showing that when you increase the amount of oral intake of glucosamine, you actually increase serum sulfate. And serum sulfate in this case is being a driver for the production of proteoglycans.

Thank you very much.

DR. ROVATI: I'm afraid I have to apologize because, besides suffering my awful Italian accent, you have also to face my bad memory, and I forgot to show you a very important slide, which is actually this one, because as I told you, we performed the follow-up evaluation in the Reginster study, but I forgot to tell you that we just recently performed the same in the Pavelka study. And this is clearly unpublished information. The data came out around four weeks ago, and we just submitted an abstract this year to

American College of Rheumatology.

This time we took 136 patients who had--we could retrieve 136 patients who had been in the trial for at least 12 months, which were 80 percent of the original cohort with these characteristics, so pretty high. Median duration of follow-up also in this case with standard of care after starting medication withdrawal was for five years. And I told you that in the Reginster study we could not see a significant difference in the number of patients with total knee replacement, which is the natural endpoint of this follow-up. But we were able to see it in the Pavelka study. You see that patients in the former placebo group had a 16-percent incidence of knee replacement--well, there were 16 percent patients undergoing knee replacement versus 4 percent, which is a decreasing risk of 73 percent, which is statistically significant.

I apologize for that, and I will go immediately to the last information that I would like to provide you today.

There are several glucosamine formulations out there. We believe that there are not enough data to support any claim, either this claim or any other claim, with these other formulations of other glucosamine salts simply because we do not have the evidence or simply because the evidence is just with the sulfate.

Also, while we have evidence, some evidence that chondroitin sulfate may work in osteoarthritis, as was noted in the previous discussion there was actually no hint of any activity of the glucosamine and chondroitin combination, either as an additive or synergistic or perhaps detrimental effect, as it may be. And this is because, I believe, it may not--this formulation may not share the same pharmacological clinical quality or PK properties of the substance that has been used so far.

Pharmacology is not a problem because you can always give to the animals as much glucosamine as you want in any salt or formulation. But the problem may be clinical and actually the only

evidence is with sulfate, crystalline sulfate, as I told you, quality, and PK is also, in my opinion, important.

With respect to treatment, I want to make clear that in the Lancet study, we were saying that the results cannot be generalized to other glucosamine products or mixtures with our compound. And I want to underline that this was a statement that was specifically requested by the reviewers because they were scared that we were generalizing it to thousands of dietary supplements in this respect. And the same statement is present in the Archives of Internal Medicine.

Quality consideration, why quality is important. Well, this formulation is regulated actually as a prescription drug in Europe and in several other countries, and so it's subject to strict quality controls. You may know that there are studies, one recently in the Journal of Rheumatology by Russell, that showed that out of 14 nutritional supplement formulations of glucosamine sulfate available in North America, only two

contain over 80 percent of the labeled glucosamine content, and for 12 formulations the stated amount ranged between 41 and 66 percent only. And these data just follow another observation, a similar observation from the University of Maryland published three or four years ago.

PK is also important because, unfortunately, the knowledge about the glucosamine PK has been limited by the poor sensitivity and specificity of the available cold chemical methods. And this, unfortunately, favored a lot of confusion in this respect, because if you cannot prove exactly the PK pattern or the PK profile of the compound, it's easy to make any claim for anything.

Luckily, very recently we were able to develop a liquid chromatography mass spectrometry detection that was validated for the determination finally of glucosamine in plasma--it was tough to develop--and allowed to study the oral bioavailability and disproportionality of the original formulation in man. And, again, these are very recent data submitted this year to the

American College of Rheumatology meeting. And I'll just show you the data, but you can actually follow very well the time course profile of glucosamine in plasma, and you can see a dose/response increase 750 or 1.5 grams once daily. It's not linear when you go over 1.5 grams, so also this is important to take into account with respect to the dose. You can calculate the half-life of elimination and support the once-daily administration that was used in the clinical trial.

Very importantly, the level that we find with a 1500-milligram dose is in the range of those that are effective *in vitro* in the chondrocyte cultures that Professor Altman has shown to you.

About significant scientific agreement, of course, we have to rely mainly on the available practice guidelines. This has been mentioned before. The very recent EULAR practice guidelines on knee osteoarthritis, this is clearly for treatment. It's not for prevention. But it's about the role of glucosamine sulfate in osteoarthritis. Glucosamine sulfate was scored the

highest level of evidence, 1A, and the highest trend of the recommendation, A. Out of 34 pharmacological and non-pharmacological modalities, this was attributed only to six of them.

In addition, glucosamine sulfate was attributed highest median quality score for trials performed, 24 out of a maximum 28, and among the highest effect size versus placebo.

What about the American College of Rheumatology practice guidelines? We have the two sides of the Atlantic, of course, and both are exactly the same as important. The problem with the American College of Rheumatology guidelines is that the last version was published in September 2000, prior to the publication of the two long-term studies, prior to the Cochrane Review, prior to the last review. And this expert committee, four experts, in which Professor Altman was included, was unable to reach a conclusion or recommendation on glucosamine. But already one year after, one of the members of the committee, Marc Hochberg, was publishing a significant paper entitled "What a

Difference a Year Makes," a reflection on his recommendation, saying that the documented efficacy of the substance requires us to reassess the use of glucosamine as a first-line agent, at least for patients with knee OA who have mild to moderate disease, which, again, goes in the direction of treatment and possibly of prevention.

Safety, all systematic reviews and meta-analyses support the safety of glucosamine sulfate in humans, and as you can easily check, the adverse event profile is really very safe, 6 percent to 15 percent incidence of patients with adverse events, dropouts in less than 4 percent, no significant difference with placebo in any trial, but significant advantage, of course, over conventional nonsteroidal anti-inflammatory drugs when you compare the drug or the compound for the treatment of symptoms of osteoarthritis.

In the two long-term trials, as you may know, the safety of the substance was similar to that of placebo. And I want to underline that being regulated as a prescription drug in over 40

countries of the world, we have to issue regular, periodic safety update reports according to ICH guidelines, and information that I gathered from here over the last five or six years estimated that out of over 30 million patients per month, there were only 200 spontaneous adverse reaction reports, with no safety signals at all.

So I would like to conclude saying that I believe we have tried to show you evidence on how the treatment data in high-quality, long-term clinical trials with glucosamine sulfate may support the claim for prevention that we've gone through. There are several clinical indications. We recognize that there is no study of prevention, and perhaps this will be difficult to obtain with anything in the near future. But there are several hints from the data published that suggest that the substance may prevent osteoarthritis, as I showed, and also the animal and mechanism-of-action models, although not enough alone, support very well the clinical data.

I thank you very much for your attention.

DR. MILLER: Thank you, Dr. Rovati.

Comments of questions?

DR. CUSH: You showed data from both trials on the need for replacement surgery of the hip or knee, although those trials were originally designed to study indexed knees. Were the same statistics arrived at when you only looked at the indexed knee? And did you have any--were any of those replacements involving contralateral knees or hips?

DR. ROVATI: Yes. In the Reginster study, actually, there was not much difference between the signal joint or the contralateral joint. In the Pavelka study, I must say that we did not perform the analysis yet because these are very new data.

DR. MILLER: Dr. Downer?

DR. DOWNER: You mentioned that there were 209 spontaneous adverse reactions. Could you clarify and tell us a little bit more what they were?

DR. ROVATI: They were mainly mild GI complaints about the patients, which are more or

less the same that we see in clinical trials, although at a very low level and similar to placebo. My report is that these patients are used to be careful to GI systems when they take anti-rheumatic medication or prevention of supplement or whatever, and sometimes they report that.

Certainly there was no other signal for any specific safety issue. For example, there was nothing with respect to diabetes, and you know that there are now several studies in humans showing that the pharmacological data on insulin sensitivity obtained in animals may not be replicated in humans. And, actually, in the Pavelka trial, for example, there were four patients developing diabetes during the study--one was on glucosamine but three were on placebo.

DR. DOWNER: I have a follow-up question to that. There were some significant improvements in the data you presented, and I'm wondering if there were any confounding variables, such as, did you see an improvement in weight, for example? Could that have impacted on some of the information

you have presented?

DR. ROVATI: No, there was no other modification in any general health status, nothing on weight, nothing on other diseases, nothing on heart rate, blood pressure--nothing at all.

DR. DOWNER: Are you saying nothing because you did look at these parameters?

DR. ROVATI: We did look exactly at this.

DR. DOWNER: Okay.

DR. ROVATI: Weight, blood pressure, and heart rate. And, of course, we looked at any worsening of co-existing diseases that in this healthy population may be present.

DR. MILLER: Dr. Abramson?

DR. ABRAMSON: I was just curious with the elevations of the sulfate that Dr. Altman showed in the plasma. When you look at your database--I'm sorry, on uric acid levels. I'm just wondering if there are any effects as an organic (?) and whether in the populations you've treated you've seen any effect through uric acid?

DR. ROVATI: I must say that we did not

look at that, so I don't know. I think there is nothing, but we did not look specifically at that.

DR. MILLER: Dr. Lane?

DR. LANE: Yes, I'm curious about a couple of the endpoints in the Reginster study and your other study. You showed that the joint space did not--the width of the joint space did not deteriorate, in fact, it appeared to increase in the Reginster study. What about other individual radiographic features of OA, such as osteophytes?

DR. ROVATI: Okay. It was actually not increasing in average in the Reginster population. There was a non-significant decrease of 0.7 millimeters, if I remember correctly. It was a bit less in intention-to-treat population of the Pavelka patients. But, clearly, there were some patients who tended to increase, as Dr. Felson mentioned before, but these were a minority.

And, sorry, your other question was?

DR. LANE: What about osteophytes?

DR. ROVATI: Okay. No, we didn't look at that in the Reginster trial because the X-rays were

sent for digitalization to London in the unit of Jane Decker, and we could not look at that afterwards, while with the Pavelka study, the analyses were performed by the investigators themselves and so they could look also at this.

DR. LANE: One more question. I'm always interested in osteoarthritis if the patients were acting the same in the placebo and the treatment group. Are there any measures of activity level, you know, what the patients were doing, you know, walking, running? Was it the same, their daily activities?

DR. ROVATI: We specifically asked at enrollment of the entry criteria that the patients should have not undergone any particular heavy activity, and also any physiotherapy or exercise had to be present and standardized before the entry into the trial. And in this respect, the two groups in both studies were very much comparable.

DR. LANE: Thank you.

DR. ROVATI: Dr. Felson?

DR. FELSON: Lovely data-based review with

a lot of data, which I know you've been very involved in. The issue here is prevention, and you were careful, I thought, and prudent about being very clear and accurate about what your data showed with respect to that. I wanted to go at that question a little bit farther in terms of the contralateral knee, which you talked about some.

You mentioned that the contralateral knee tended to have pretty large joint space at baseline in both of the studies. The issue here is whether the contralateral knee had OA, because if that were the case, then there would be evidence that this was a treatment in established OA as opposed to a treatment of a joint that was unaffected.

Most people with knee OA, 60 percent roughly, have bilateral disease, not unilateral disease. So do you know the Kellgren and Lawrence grade of the contralateral knee?

DR. ROVATI: Yes, it's an excellent question, of course, and we looked for minor signs of osteoarthritis and--minor signs of osteoarthritis such as initial doubtful

osteophytes, I may say, that were present in most of these patients.

With respect to Kellgren and Lawrence, we were not able to give to them a Grade 2, but there were minor signs of osteoarthritis.

DR. FELSON: So remembering, just for the committee, that by the time you get radiographic disease, radiographic disease is a fairly late structural finding of osteoarthritis. So the fact that there were small osteophytes in most of the contralateral joints suggests that there was existent disease in those contralateral joints.

Now, that begs the question of sort of when is incident disease, which is a very difficult question that we could probably spend another week on and not get the answer to. But in another recent trial, one that was presented at ACR, of doxycycline, another potential remittive or disease-modifying therapy, in which there was a great attempt to get unaffected contralateral knees, they made a very strong comment at the end of the day that they were pretty much unable to get

unaffected contralateral knees, that, in fact, when they looked closely at the contralateral knees, they all had some measure of osteoarthritis.

So for the purposes of thinking about prevention, I would just take those arguments into account perhaps.

DR. ROVATI: You're totally correct. As I was saying, probably these patients could be classified as Kellgren and Lawrence Grade 1, which is doubtful osteoarthritis. I agree with you.

DR. MILLER: Dr. Krinsky?

DR. KRINSKY: I think Dr. Felson has addressed the issue that I was concerned about, and that was the two studies where you used the data with respect to the contralateral knee, and the Pavelka study shows no significant difference. So I assume you can discard that.

And if we look at the Reginster study, the placebo group seems to be advancing at a much more rapid rate than what's been referred to as the normal group. So can we describe that as a normal knee? Can we use that as a normal knee joint?

DR. ROVATI: Yes, thank you very much. It's an excellent question. Actually, these data in the Reginster trial are consistent with the quartile analysis that I showed. The patients that were--in a signal joint that were progressing were those in a better joint state at enrollment. And so the contralateral knee, at least in this particular cohort, that had an even better preserved joint space, was progressing even more. So this is consistent throughout this patient population.

With respect to the Pavelka trial, you're totally correct, and I have underlined that the data were not significant. But you also have to note that although the difference with placebo in the Pavelka trial was of the same magnitude as in the Reginster trial, they tended to progress a bit less. And, actually, we noted--and it's published--that these patients were a bit leaner than in the Reginster population. And overweight may be a risk factor, and this is why we may see more progression and more prevention of disease in the Reginster

trial than in the Pavelka study.

DR. KRINSKY: Thank you.

DR. MILLER: Dr. Mehendale?

DR. MEHENDALE: In your pharmacokinetic studies, you reach peak plasma levels rather quickly. Do you know--and it drops rather quickly. Do you know anything about the distribution of this compound in the target tissue?

DR. ROVATI: Yes. This, of course, we could not do yet in humans. We are trying to validate the method, at least in synovial fluid, to see what we have there. But it's not been developed yet.

We have early animal data that have been reported before by the previous petitioner in which we uniformly labeled glucosamine with C14 on a carbon ring. And, actually, with autoradiography, after administering the compound by the oral route and taking autoradiography of the intact rat, we saw that the compound was concentrating--well, was very much in the liver because, of course, the liver represents a first--has a first-pass effect,

and then was concentrated specifically in the joint areas that we could analyze. But, of course, we have no data in humans. This is very clear.

DR. MEHENDALE: Can you give us some idea what percent of either dose or relationship to plasma levels might be found at the cartilage tissue?

DR. ROVATI: We currently estimate, based on this new data, that the absolute bioavailability, although we do not have an absolute bioavailability yet, is around 20 to 30 percent of the oral dose. And the previous animal studies have shown that, compared to blood, it concentrates five times more in the cartilage with respect to the blood itself or other organs.

DR. MEHENDALE: I have a question about the *in vitro* studies where you showed--Dr. Altman's studies, where he showed effects on number of signaling molecules. My earlier question relates to this, to see the levels that he used in these *in vitro* studies to show effects on signaling events, how they might relate to the levels you find *in*

vivo. I don't know if you might have some information that you might shed some light on.

DR. ROVATI: Probably I was very quick on that, but the actual levels that we found in plasma, especially if you consider that, according to our early data, the compound concentrate in the cartilage, they are pretty much in line with what Dr. Altman has shown as an effective concentration at the chondrocyte level in culture.

DR. MEHENDALE: And one more question. I wonder if you know what the effects might be in normal tissue then with those levels on the signaling events in the cartilage tissue.

DR. ROVATI: Dr. Altman, do you want to take that?

DR. ALTMAN: Go ahead.

DR. ROVATI: Actually, the data that Altman has presented to you, there are two particular studies as shown *in vitro*--one which was from an independent Spanish group and one which was obtained in our lab confirming the findings. And, actually, the results are very much superimposable,

but the real difference is that they used osteoarthritic chondrocytes taken from osteoarthritis patients, and we took an absolutely normal chondrocyte from animals. So the effect, when you stimulate the chondrocyte with a strong pathogenic factor such as interleukin-1, seems to be the same irrespectively whether the chondrocyte is already osteoarthritic or is normal.

DR. MEHENDALE: This applies to COX, INOS, as well as signaling molecules, NF-kB--

DR. ROVATI: Exactly.

DR. MEHENDALE: Uniformly on all of those?

DR. ROVATI: Exactly, because we believe that the main pharmacological activity of the compound is actually to inhibit or reduce the translocation of active NF-kappa B that then stimulates the expression of COX-2, INOS, metalloproteinases and so forth, and we actually so the same in healthy or osteoarthritic chondrocytes.

DR. MEHENDALE: Right. To extend this a step further, I wonder what the implications might be to a normal tissue, normal cartilage, upon

repeated decreases in these molecules, obviously in the absence of any disease.

DR. ROVATI: Yes, it's an excellent comment, of course. We believe that there is--as was said also by the previous speaker, by the previous petitioner, when you simply administer glucosamine to healthy chondrocytes or healthy animals, you simply see no effect or at least no effect that we can detect. The only effect you see when you stimulate, for example, *in vitro* even the healthy chondrocyte with a pathogenetic factor. So that's why we believe that the preventive issue may be supported by that, because when the pathogenetic factor enters into play, then you can prevent it from exerting its effects. But in the normal cartilage, in normal animals, you actually have nothing.

DR. MEHENDALE: One limitation of those *in vitro* studies, of course, we don't have an opportunity to look at repeated exposures on normal tissues. And, therefore, we are kind of walking an unknown bridge, so to speak, when we translate into

in vivo effects.

DR. ROVATI: I take your point.

DR. MILLER: Dr. Zeisel?

DR. ZEISEL: Getting back to Dr. Felson's point about contralateral knee not necessarily being normal, as a non-rheumatologist, could you help me? Of the 20 to 25 members of this panel who do not think they have arthritis, how many of them have abnormal osteophytes, for instance, on their knees?

DR. LANE: How many have had their knee X-rayed?

DR. ZEISEL: Well, how many would you guess from your look at normal individuals who don't come in with a complaint of osteoarthritis?

DR. FELSON: That's a really--it's not a hard question to answer, but its interpretation is pretty tough. So I can tell you, as the head of the Framingham Osteoarthritis Study, a sub-study of the Framingham Heart Study, in which we've just obtained MRIs on a lot of normal people age 45 and over, that nearly 100 percent of knees of people

age 45 and over have tiny, or larger, osteophytes, many of which are not visible on the X-ray.

One of the reasons we use the X-ray as our way of defining disease is mostly historical, but also because it actually provides a threshold level of size of osteophyte that tends to help us distinguish between those with pain and those without pain reasonably well. So those tiny little things that we see on the MRI usually aren't the threshold level above which--I don't know if there's meaning to the definition. I'm not sure there is, but if there is, that would be it.

There's a different question here, though, which is: Is prevention for a health claim, which I think is probably what we're supposed to talk about here, the prevention of contralateral disease in someone who has unilateral disease, or is it prevention of the new onset of disease in someone who doesn't have disease at all? And I think we're increasingly aware of the fact that this is a bilateral and often systemic process and that the presence of clinical disease in one joint is either

a harbinger of or goes along with clinical disease in its contralateral partner. And I think it would be--I don't think these are people who have contralateral joints which are the same as your joints, assuming that you don't--that you have those tiny little osteophytes that we all have.

DR. ZEISEL: Okay. But, again, the point I am thinking about is that if almost 100 percent of the members of this panel have pathology on their knees which would not have been there when they were probably 17 years old and we're dealing with chronic diseases that have a continuum, it is a leap of faith both to argue that they are the same as what the person has in the osteoarthritis, but it's also a leap of faith to argue that they aren't part of the early continuum, that if you followed those individuals from the Framingham Study and looked at them 15 years later, many of the ones who have more osteophytes went on to have the early stigmata of osteoarthritis.

And so if that's the case, then the contralateral knee argument that's being made is as

close as you can get to extracting data that's clinically already there that may be useful.

DR. MILLER: Actually, another way of putting it--and it's a matter that we can discuss tomorrow--is in order to--one of the questions we need to deal with is what is the kind of data that would be needed in order to demonstrate that a prevention claim can be made. And it seems to me that the big argument is what constitutes the baseline. I wouldn't call it normality, but what constitutes the baseline. And that should be one of the questions we ought to be discussing tomorrow.

Dr. Russell?

T7 DR. RUSSELL: I had questions more or less along the same lines that have been discussed now.

DR. MILLER: Dr. Callery?

DR. CALLERY: This is a question back to the compound that you've been discussing, and thank you for pointing out that most of the studies done were done with compounds that were not well characterized and probably not what they said they

were in the process. But let me ask a question about your compound in particular.

If you had an equal molar amount of your complex versus pure glucosamine free base or glucosamine hydrochloride, would you expect a better response from your compound?

DR. ROVATI: There is certainly the factor of sulfates, and as Professor Altman mentioned, we do not know exactly how much sulfates are important. They're clearly important in the metabolism of cartilage. Whether they significantly increase the pharmacological activity of glucosamine sulfate is not known at present. The only data we have is, again, the clinical data with glucosamine sulfate.

So I think that your point is well taken. So if you exclude the sulfates and you provide the primary active ingredient, which is clearly glucosamine, I think you should--you may get similar effects, as long as this different formulation has the same pharmacokinetic properties and as long as you can actually, since there is

this uncertainty about sulfate, you show some kind of therapeutic equivalence or something, some hints that lead you to think that the effects may be the same.

DR. MILLER: Dr. Blonz?

DR. BLONZ: I think that the European regulation as a drug is informative. As we get closer to the lunch break, I want to step back a little bit and talk about the substance itself. We're talking about food here. We're not dealing with drugs. And we are talking about putting this in the food supply.

Now, according to the Federal Food, Drug, and Cosmetic Act, for something to be added it's got to be a food. It's got to be a food substance. And according to your petition, we're talking about a substance that's a vitamin, mineral, herb, or other similar nutritional substance, specifically food or a component of food.

So what specific food or component of food do you find crystalline glucosamine sulfate?

DR. ROVATI: You do not find crystalline

glucosamine sulfate. You find glucosamine or you find the glucosamine sulfate incorporated in the tissues in any food that contains cartilage or perhaps--well, connective tissues.

It's clear that the regulations in the U.S. and in Europe are quite different in this respect because the U.S. has a specific regulation of food supplements or dietary supplements that are regulated as a drug in Europe because there is not any provision for food--they're starting to arrive, but there's not any provision. So whatever you show in Europe, automatically you are a drug. You do not have the option of having a food supplement.

DR. MILLER: Dr. Cush?

DR. CUSH: I just want to make the statement that I think Dr. Felson's comments are very helpful, and we do know that X-rays will show progressive evidence of osteoarthritic change in a population as it ages. But it's also important we teach to our students and to primary care doctors that there's a real disconnect between symptoms and X-rays. And, hence, you know, making decisions

solely based on radiographic and imaging studies about joint space narrowing and whatnot may not--is still a big leap to actually symptomatic disease.

DR. MILLER: Dr. Kale?

DR. ROVATI: Can I comment on that, Dr. Miller?

DR. MILLER: Sure.

DR. ROVATI: You're perfectly right. It's clear that symptoms and structure do not go in the same direction, at least in the early stages. When you then arrive to the point of joint surgery, you have a severely damaged joint and you have symptoms.

But this is absolutely extremely important, and actually I did not show about the quartile analysis in the Reginster cohort showed that, while only those more (?) were progressing in joint space loss, both were progressing in symptoms and the compound was effective in both on the symptoms of the disease. So it's clearly something which is divergent. Perhaps until the very late stage when the two go to the endpoint or

final clinical outcome.

DR. MILLER: Dr. Kale?

DR. KALE: A number of comments, but most recently, the comment made by Dr. Miller forces me to ask what may be a theological question, and that is: Who are the proper subjects for this product? If we can't agree when osteoarthritis begins in an adult and if the data that you've collected in your studies looking at now MRI scans suggests that disease is virtually everywhere, then where is it not everywhere, radiographically or otherwise? Who would serve as appropriate subject for this nutritional product? Would it be something like a vaccination, we start at birth? When would one start?

DR. ROVATI: Certainly the therapeutic data available support the fact that the substance is particularly effective in mild to moderate osteoarthritis. This is clear, although the symptoms can be treated also in more severe stages in the short-term clinical trials, reviewed in the meta-analysis support that. I think I tried to

show you that this mild osteoarthritis can be probably brought a little backwards and we can treat patients--or we can supplement subjects that are at risk of osteoarthritis.

DR. KALE: The question is how do you determine who--everyone's at risk, which is why you end up vaccinating everybody. Everybody's at risk, because we all are. How do you decide? And if the issue here is prevention, then the question is preventing when, in whom, how?

DR. ROVATI: It's an excellent question. I'm not that expert to reply precisely to that. I would say patients who may be at risk because of physical activity, because of weight, such as obesity, or simply because, for example, in an X-ray they have minimal signs of osteoarthritis which is not yet clinically significant and this may be helpful.

DR. MILLER: Dr. Abramson?

DR. ABRAMSON: These are difficult questions, and I guess as a rheumatologist it's important to frame this in the context of where the

field is. And for those people who are not rheumatologists, the NIH, as we heard very early on, is spending millions of dollars to study 5,000 people to, in essence, address this kind of question, people with very early disease, what happens to them over five years or longer, with the presumption being that most do very well and don't need any intervention of prevention. But the answer is the fact is that the field--these are unknowns in the field. So I think what we're grappling with is how do we pretend to know the answer today when we're not going to, at least academically, to the extent that the OA initiative can address that, won't know that for five years.

And I guess that raises a question or a clarification for me as we each struggle with this that does touch on regulatory. Here we have a compound that's synthesized, that has a mode of action that looks like a drug, inhibits NF-kappa B like corticosteroids do, that now would be--it is a drug in Europe, and then we are--so if we were addressing this as a drug in the U.S. across the

street at CDER, we would be asking for the clinical evidence that it prevents.

So how do we wear two hats here? And I guess this is kind of a regulatory question. Can it be a food here where we apply a different set of standards than if this meeting were happening in this hotel, you know, two years from now, if you filed an IND or something, or an NDA, would the discussion be different and should it be different? You know, this is where I think a lot of us are trying to understand the process at this committee rather than at the arthritis--

DR. MILLER: The decision concerning how this is to be regulated is made by the agency, as far as I can tell. Our concern is the science, irrespective whether it be regulated as a drug or as a food. The difference is that the law defines foods--defines supplements as foods, and that complicates the issue, but not for us. Our issue, the issue that we're supposed to deal with is: Is there sufficient data to support the idea that this prevents osteoarthritis? And if not, what data

would be needed in order to do it? That's the kind of question--how that ultimately gets used is a matter for the agency and the lawyers deal with. That's something we just can't--I hope to God we don't ever get involved in.

[Laughter.]

DR. MILLER: Nothing personal to my friends in the agency.

Dr. Espinoza?

DR. ESPINOZA: I was wondering, since this compound also relieved pain, if there is any data about its use in other populations, in younger patients, rheumatism, fibromyalgia, especially in Europe.

DR. ROVATI: There are some early data on chondromalacia of the patella, but I would be reluctant to take them as evidence of their activity in this kind of disease because these were really early data produced over 20 years ago when clinical trials were clearly not of the same standard as of today. So today there is no new study in this respect.