

activity with typical oral dosages, and that's over a short term.

Now, if you can extrapolate the effects of doing that over and over and over and over and over again for years, I think that can easily explain the cessation of loss of cartilage. If you're stopping the inhibition and improving the synthesis, what else can happen?

How much more time do I have? I want to make sure not to run over. Okay, thank you.

I also wanted to mention other biomarkers affected by chondroitin, one of which is mechano-structural or tensegrity for tension integrity. Chondroitin being a highly charged molecule and accounting for a lot of the structural integrity of cartilage itself, when it is lost, that structural integrity is lost, more mechanical forces are transmitted to chondrocytes. They do have mechano-receptors as part of what their cytoskeleton is there for. So when cartilage is lost, chondrocytes have another way to determine that. They don't need the fragments. They can just see the overall

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 cytoooxygenase 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 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/creatinine 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 agrosopic 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