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AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

**ORTHOPEDIC AND REHABILITATION DEVICES PANEL
OF THE MEDICAL DEVICES ADVISORY COMMITTEE**

Volume I

Thursday, March 6, 1997

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 OF CLINICALLY SIGNIFICANT ARTICULAR CARTILAGE DEFECTS
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P R O C E E D I N G S

MS. NASHMAN: Good morning, everybody. It looks like our panel is assembled. We are ready to begin the meeting of the Orthopedic and Rehabilitation Devices Panel.

My name is Jodi Nashman and I am the executive secretary of this panel and a reviewer in the Orthopedic Devices Branch.

I would like to remind everybody that you are requested to sign in on the attendance sheets which are available at the tables by the doors. You may also pick up an agenda and information about today's meeting including how to find out about future meeting dates through the advisory panel phone line and how to obtain meeting minutes or transcripts.

Please note that any information displayed on overheads or slides is not directly available from this group of FDA. Information can be obtained either by requesting the transcripts of this meeting and information about that is provided at the desk outside or by requesting the information by the Freedom of Information process.

Today, at the request of and in conjunction with the Center for Biologic Evaluation and Research, the committee will discuss Carticel (autologous chondrocytes manipulated ex vivo for structural repair Genzyme

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Corporation) intended for treatment and repair of clinically significant articular cartilage defects in the knee.

At this time I would like to turn the meeting over to Dr. William Freas and Dr. Edward Hanley, who is the panel chairman.

Have a nice day and I will see anybody tomorrow.

Opening Remarks

DR. FREAS: Good morning. I am Bill Freas and I will be the Designated Federal Official for this morning's meeting. I would like to welcome the members of the public that have joined us this morning, the members sitting at the table, and everybody from CDRH who has helped us put this meeting on.

At this time I would like to go around the head table and introduce to the audience the members seated at the head table. We will go around starting on the left side of the room, that is the audience's left side of the room.

If the committee members would raise their hand when I call their names, so the audience can identify you.

The first seat is occupied by Dr. Gary Friedlaender, who is a consultant for today's meeting. He is Professor and Chairman, Department of Orthopedics and Rehabilitation, Yale University.

The next individual is Dr. Raymond Silkaitis. He

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is our Industry Representative for today. He is Vice President of Medical and Regulatory Affairs, Gliatech, Cleveland, Ohio.

Next is Dr. Leela Rangaswamy. She is a member of the Orthopedic Committee. She is also Deputy Editor, Journal of Bone and Joint Surgery.

Next is Dr. Roger Nelson. He is a consultant for today. He is Professor and Chairman, Department of Physical Therapy, Thomas Jefferson University.

Next is Dr. Daniel Clauw. He is a consultant for today. He is Chief, Division of Rheumatology, Immunology, and Allergy at Georgetown University.

Next is Dr. Stephen Trippel, a consultant for today. He is an orthopedic surgeon from Massachusetts General Hospital.

Next is Dr. William Tomford, consultant for today. He is Associate Professor of Orthopedic Surgery, Harvard Medical School.

Next is Dr. Klaus Kuettner. He is a consultant for today. He is Professor and Chairman of Biochemistry, Rush Medical College.

Next is Dr. Keith Markolf. He is a committee member. He is Professor of Surgery, Orthopedics and Biomechanics, UCLA Rehabilitation Center.

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Next is Dr. Robin Poole. He is a consultant. He is Director, Joint Diseases Laboratory, Shriners Hospital for Crippled Children in Montreal.

Next is our committee chair, Dr. Edward Hanley. He is also Chairman, Department of Orthopedic Surgery, Carolinas Medical Center.

The next seat will be occupied by myself.

Next is Dr. Clement Sledge. He is a consultant. He is Chairperson of the Physician Hospital Organization in Boston.

Next is Dr. Seth Greenwald. He is a consultant. He is Director of Orthopedic Research, Mt. Sinai Medical Center.

Next is our Consumer Representative, Dr. Doris Holeman. She is a nurse, Albany State College.

Next is Dr. Clinton Miller, a consultant, a retired Professor and Chair, Department of Biometry, Medical University of South Carolina.

Next is Dr. Richard Coutts, a non-voting consultant for today. He is Professor of Orthopedics, University of California.

Next is Dr. Hugh Auchincloss, a non-voting consultant for today's meeting. He is Associate Professor of Surgery, Harvard Medical School.

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Dr. Michael Mayor, who is on your agenda this morning and on the list of committee members as a consultant, is not here today. He called in last night saying that he was stuck in New Hampshire in a snowstorm.

At the table there are also two FDA individuals. They are here to help us with the conduct of the meeting. They are Dr. Jay Siegel, Director of Office of Therapeutics, Research & Review, and Dr. Kathryn Zoon, Director of Center for Biologics Evaluation & Research.

I would like to welcome everybody here this morning.

I would now like to read into the public record the conflict of interest statement for this meeting.

This announcement is made part of the public record to preclude even the appearance of a conflict of interest at this meeting of the Orthopedic and Rehabilitation Devices Panel on March 6, 1997.

Pursuant to the authority granted under the committee charter, the Deputy Commissioner for Operations, Food and Drug Administration has approved the following individuals as temporary voting members: Drs. Daniel Clauw, Dr. Seth Greenwald, Dr. Michael Mayor, Dr. Clinton Miller, Dr. Roger Nelson, Dr. Gary Friedlaender, Dr. Klaus Kuettner, Dr. Anthony Poole, Dr. Clement Sledge, Dr. William Tomford,

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and Dr. Stephen Trippel for the CBER-sponsored topic on March 6th.

Dr. Barbara Boyan, a committee member, has recused herself from discussions on March 6th. She will be participating in discussions on March 7th.

Based on the agenda made available and all relevant data reported by the participating members and consultants, it has been determined that all financial interests in firms regulated by the Center Biologics Evaluation and Research that may be affected by the committee's decision as of this date present no potential for an appearance of a conflict of interest at this meeting with the following notations for the record.

In accordance with 18 U.S.C. 208(b)(3), Dr. Hugh Auchincloss and Richard Coutts have been granted a limited waiver which permits them to participate in the discussions of the BLA for Carticel, however, they are not permitted to vote on this issue. In addition, Dr. Seth Greenwald has reported that his research laboratory receives support from an unrelated orthopedic firm not directly related to today's discussion.

The statements above were the result of screenings conducted to prevent the appearance, real or apparent, of a conflict of interest.

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Copies of the waivers are available by written request under the Freedom of Information Act.

In the event that the discussions involve other products or firms not already on the agenda for which FDA participant have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusions will be noted for the public record.

With respect to all other meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firms whose products they may wish to comment upon.

So ends the conflict of interest statement.

Dr. Hanley, I turn the meeting over to you.

DR. HANLEY: Good morning. My name is Dr. Edward Hanley. I am chairperson for this panel. I would like to thank everyone for coming this morning, however, I would note we have a very full agenda and in order to allow the committee sufficient time to discuss today's issues, I would like to ask all participant speakers to strictly stick to their allotted times.

As part of the advisory committee meeting there is an open public hearing for members of the public who would like to make a statement concerning the matters pending

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before the committee. Dr. Freas has received eight responses to the Federal Register announcement requesting to speak.

Because of the number of speakers, I would ask that everyone limit their presentation to a maximum of five minutes in order that everyone has the opportunity to speak at the podium.

Open Public Hearing

DR. FREAS: Dr. Hanley, I have received the follow list of speakers. If these speakers would please come to the podium or use the microphone in the center of the room at this time. Let me, first of all, read the list and this is the order in which I am asking them to come to the podium.

They are: Mrs. Sharon Clayton, Mr. Gerald Trombly, Mrs. Jan Curtis, Mrs. Nina Winer, Mr. Donald Pascale.

Before you start, Sharon, let me just make one further statement. Would all speakers this morning in the interest of fairness address any current or previous financial involvement with any firm whose products you may wish to comment upon. This financial involvement would include travel or reimbursement for expenses coming to this meeting. We request that if you don't have any conflicts,

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please so state as well.

For the speakers, they will be given a green light for four minutes followed by a yellow light. When the yellow light appears we ask that you conclude your presentation.

Go ahead, Sharon.

MS. CLAYTON: Hello. I am Sharon Clayton.

Genzyme did pay for my travel expenses to come, but I would like for everybody to know that I flew directly from Hong Kong early to be here. I was on vacation there and it was my choice to come.

I am 33 years old now. At 25 years old I was a professional ballet dancer, as well as a vice president of a global Fortune 100 company, and at that point my life began to significantly change because of the knee pain that I was experiencing.

I had five different surgeries trying to alleviate the pain that I was experiencing, no longer able to dance, no longer able to do any form of exercise and definitely affecting my work and having to spend an awful lot of time not walking, not standing, a tremendous amount of pain.

No painkillers, no surgery, nothing could take care of it, so for about seven years I spent 99.9 percent of my time having basically what I would call daggers in both

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knees and just had to really kind of just deal with it every day.

Because I am a Type A personality, I continued to work as much as I possibly could. I continued to try to do things to keep my body in shape. I saw every doctor possible in any country I could possibly hear of anything that would help me, and there was absolutely nothing anybody could do.

I heard about the Carticel procedure on NBC News about two and a half years ago, called Massachusetts General where they were bringing it over from Sweden, and I began discussing my case with them. They said I was a perfect candidate.

It took me about two and a half years after that because I could not get it approved by my insurance company, still did not get it approved by the insurance company.

In the meantime, I moved to San Francisco, found a doctor who was also doing the surgery, continued to read every article I could get my hands on about it, listened to lots of people who have talked about it, experts, non-experts, people who had the same thing I did, and found a doctor that was going to do it, would do it without my insurance company paying for it, and my husband and I ended up paying for it because it meant that much to us to have it

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done.

My whole life has changed. I spend about 99 percent of my time now without pain, eight months after surgery, and I had both done at the same time, and it is the best thing I could have ever done, and I would do it again 10 times over, and I would pay for it again 10 times over.

So thank you very much for letting me speak.

DR. FREAS: Thank you, Sharon. Our next speaker is Gerald Trombly.

MR. TROMBLY: My name is Jerry Trombly. I am also here with Genzyme. They are paying for my travel and lodging, but I would like to point out that I am taking vacation time from my work to be here.

In the fall of 1994, my left knee completely gave out. I had prior knee problems, but at that time it completely failed. I had been told by a number of surgeons that I needed a total knee replacement.

At that point I was living in chronic pain. I was on pain pills and anti-inflammatories. My social life didn't exist any longer, my family life didn't exist either. I could only work a few hours a day, and the rest of my time was spent either lying in my bed or lying on my couch. Any weight on my knee would cause severe pain. So my lifestyle was very, very limited at that point.

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At one point I was told by my physical therapist that I needed to consider at that point I was disabled. Forty-four years old, it was very difficult for me to hear that, disabled.

In September of 1995, I was given the opportunity to have cartilage replacement. I refer to it as my miracle. Today, it is like a miracle. You certainly can't tell my seeing me, I walk very well, but I walked with a permanent limp continually, and as I said, the pain was unbearable.

Today, I can ride a bike. My goal through the surgery was to be able to walk. I was asked by my physician would you like to be able to play sports or jog. I said I would like to be able to walk without pain. I have achieved that. In fact, now when my wife and I go for a walk, she can't keep up with me. That is how well I have progressed.

My hope today is that other people that are living with the kind of chronic pain and knee injuries that I have experienced, that they too can have a miracle in their life

Thank you.

DR. FREAS: Thank you.

Our next speaker is Jan Curtis.

MS. CURTIS: Hi. My name is Jan Curtis, and I want you to know that GTR has covered my travel expenses here today, but if they had not, I would have paid for it on

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my own anyway. That is how important this is to me.

I am here today to talk about my articular cartilage injury and how it has affected my life. This injury has permanently affected me. For the past 18 months since I injured myself, my life has not been the same.

I played on the women's professional racquetball tour, which I can no longer play because of this injury. I love sports more than anything and I am extremely limited as to what I can do. Even walking on the treadmill has been painful for me.

I am also a flight attendant and am on my feet sometimes for up to 14 hours a day, and by the end of the day my knee is swollen and stiff. I have lost many months of work without pay due to this injury.

My insurance company denied paying for the tissue transplant even though they told me they thought it would be very promising, since it was not FDA-approved, they would not pay for it. I have had all traditional treatments for this injury including two abrasions with no success.

My recent one showed my defect has gotten worse. If I had the money myself, I would pay for this, but I don't. So, I hope that you sincerely consider approving this tissue transplant to help alleviate my suffering, which I live with daily.

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Thank you.

DR. FREAS: Thank you.

Our next speaker is Ms. Nina Winer.

MS. WINER: Hi. My name is Nina Winer. Genzyme Tissue Repair paid for my hotel and travel to be here today. I am missing my work. I am not being paid for this.

This container contained the cells that brought me back a normal life. I am so thankful that this was made available to me. I have always had an active life. I previously was a dancer. I have always enjoyed hiking. I am the mother of young children, and I found suddenly, in October of 1995, when I was struck with osteochondritis dissecans that everything became painful, any movement of my left knee was excruciatingly painful. My kids saw me cry for the first time in my life. I walked across the street and suddenly my life changed.

Any pressure at all on my left side with my knee bent meant I was in agony. I could not sit. I could not walk. I could not shift position. I couldn't sleep. Painkillers did nothing to take care of the pain.

The orthopedic surgeon that diagnosed the osteochondritis dissecans gave me a dismal prognosis. He said that arthritis would set in and that in most likelihood I would become disabled from the condition. At the time I

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was 39 years old.

In my family, there is a lot of longevity, and that meant with knee replacements, I would have needed four or five of them. In November of 1995, I had arthroscopic surgery to debride the bone and remove the bone chip.

My surgeon applied for authorization for autologous chondrocyte implantation in December. In January, my HMO approved this. In February, the HMO rescinded the authorization. In March, I lost an appeal and then in April I took it to a grievance procedure which I won with the help of a lot of wonderful people in the State of New York that helped me fight politicians, state officials.

We did a big battle and as a result, I became the first patient in the State of New York to get a major HMO to cover autologous chondrocyte implantation.

This has made a major difference in my life. I can walk, I can do stairs. By eight weeks after the surgery, already I was better off than I was before. I didn't need a cane anymore. I didn't have the pain at every slight movement.

By five months after the surgery, I was able to walk stairs, I was able to walk distance, and I could return to a normal life, and I just want to make sure that this is available for other people, please.

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Thank you very much.

DR. FREAS: Thank you, Nina.

Our next speaker is Donald Pascale.

DR. PASCALE: Good morning. My name is D.J.

Pascale from Atlanta, Georgia, and I am the luckiest guy in the room. I am little shaken up right now, but I have got to tell you guys I am not going to bore you with my life before the surgery, but I will tell you I had the surgery two years ago, I am 6 foot 4, 280 pounds, I do aerobics three times a week, step, low, and high impact aerobics. I am the catcher on a softball team, and my life has been turned around since having this procedure.

Genzyme has paid my way up here, however, I own a small printing business. We are in the height of our season. We are backed up, I have got customers screaming at me, so this trip has cost me more than the plane fare up here.

I am just -- I am a happy camper. This is a no-brainer. There is some 400 people who will benefit from this surgery, and if they have the results that I have, that's wonderful.

So I want to thank you for letting me talk today. I would be happy to answer any of your questions. That's it.

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DR. FREAS: Those are all the patients that have responded to our FR notice.

Are there any patients in the audience who would like to address the committee at this time?

[No response.]

DR. FREAS: If not, Dr. Hanley, there are three physicians that have responded to our request, and they would like to address the committee.

I would like to introduce them in this order. Dr. Scott Gillogly.

DR. GILLOGLY: Would you put the first slide on, please.

Hi. I am Scott Gillogly. I am a practicing orthopedic surgeon from Atlanta, Georgia, and I appreciate the opportunity to address this distinguished panel.

[Slide.]

First, I would like to discuss my early clinical experience with autologous chondrocyte implantation. First, I would like to discuss a little bit my personal basis for selecting this treatment.

I trained at Walter Reed here in Washington, D.C., and had my initial orthopedic practice in the military, and I was impressed with the number of young, aggressive patients who I would see with very destructive cartilage

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lesions that would be progressive at a very young age.

Additionally, I was not pleased with my own personal experience with traditional treatment methods and felt that the literature adequately documented the inadequacies of these treatment methods and also for certain considerations it was not even a recommended treatment.

Because of this experience we did a study in the early 1990s looking at really what the effect is of what we are trying to accomplish with cartilage repair, and that is to prevent the destruction of proteoglycan fragments, chondroitin sulfate, and keratin sulfate into the joint leading to degenerative arthritis.

[Slide.]

We did a prospective study of 25 patients with chronic ACL tears and measured the keratin sulfate and the total sulfated glycosaminoglycan in the synovial fluid in both the injured and the control knees, used monoclonal antibody in dimethylene blue dye binding assay.

[Slide.]

We took the fluid from the normal knees, as well as the involved knees. We showed a statistically significant increase of 88 percent for keratin sulfate and 83 percent for the glycosaminoglycan, and the most important thing is that there was a correlation with grading of the

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degree of chondral defects within the knee, and this also correlated with increased uptake on bone scan and radiographic findings of early arthritis.

[Slide.]

Because these patients, many had been treated with traditional treatment methods, and it is obvious biochemically had continued to deteriorate within their knees, I looked for additional treatment options for these patients.

I approached Genzyme Tissue Repair in late 1994 to begin trying this method. I was impressed with the published and frequently updated results that have come from Sweden, and I was particular impressed as an orthopedist by patients who had late improvements in the results, better at 18 months than they were at 12 months, something that I had never seen with a traditional type treatment.

Furthermore, with longer follow-up, there was no decline in results, something that we have been too familiar with, with our traditional treatment methods. The goals of the procedure for my patients have been improved pain and function with activities of daily living and work activities, restore more normal natural history, improve function for low-impact cardiovascular fitness, and ultimately allow recreational sports.

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[Slide.]

I have done 27 patients and 35 lesions that range from 14 to 52, predominantly males; 19 of the patients had a total of 34 previous surgical procedures.

[Slide.]

The breakdown is pretty much as you would expect, predominantly femoral condyle lesions, 2 each were osteochondritis dissecans of both the medial and the lateral femoral condyle.

[Slide.]

The average size, quite large actually, 6.12 square centimeters. but it ranged up to 17 square centimeters. Here is a defect, osteochondritis dissecans involving almost half of the lateral femoral condyle, and this is periosteum in place.

[Slide.]

At the time of biopsy, meniscal and condyle debridement were accomplished. At the time of autologous chondrocyte implantation, three patients underwent ligamentous reconstruction. Eight patients had anteromedialization of tibial tubercle, and one a high tibial osteotomy.

[Slide.]

Early results, 3 to 20 months, 19 of 21 patients

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achieved full range of motion by 12 weeks, 14 of 16 patients at six months were markedly improved.

[Slide.]

There were two problems. Both of my complications had been arthrofibrosis or motion problems, both females, but both were salvage type knees in patients where clearly there were no other options. One patient underwent a four defects graft at the same time. The other one underwent a large defect with high tibial osteotomy. Even in the arthroscopic lysis of these adhesions, we were able to learn.

[Slide.]

Here is one of the patients, femoral trochlear lesion. You see the articular cartilage flap and the exposed bone below.

[Slide.]

At the time of her debridement, here is the same defect with a glistening type appearance of hyaline-like cartilage responding to the probe very similar to the surrounding tissue.

[Slide.]

At one-year follow-up with 11 patients, you see the improvement in the symptom rating scale for pain, swelling, and buckling. Certainly a marked improvement as

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these patients can attest to.

[Slide.]

Using the Knee Society Clinical Rating System, had marked improvement at six months, but more importantly, continued improvement at one year. This is my first 10 consecutive patients, and to have this kind of result in a Knee Society Clinical Rating System is something that I have never seen or never seen reported in the literature for traditional type treatment methods for these size defects.

[Slide.]

Overall, the patients show increasing activity levels. The patients are all satisfied and feel that the goals of the procedure have been met. Activities that they have returned to include tennis, including college football, roller blading, and aerobic type activities.

[Slide.]

I believe that this is a demanding but clearly reproducible surgical procedure. The effects of the concomitant procedure are very minimal, and there is a high degree of patient satisfaction.

[Slide.]

The goals of the procedure have been met in 91 percent of the patients who were out longer than one year. The results are better and more consistent than traditional

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treatment methods, and I feel that my early results mirror the long-term Swedish data, and I can only anticipate continued good results of these patients.

Thank you.

DR. FREAS: Thank you.

Our next speaker will be Dr. Lars Peterson, Associate Professor, Goteborg Medical Center.

DR. PETERSON: I would like to thank the committee for allowing me to present my experience of autologous chondrocyte transplantation before this distinguished panel.

[Slide.]

I would like to share with you today our clinical experience of one to nine years of autologous chondrocyte transplantation in the human knee.

[Slide.]

We have since the New England Journal of Medicine article with 23 patients published, we have operated more than 375 patients with this technique. We have reassessed every patient from the beginning, and more than 116 patients have now passed the minimum of two years.

We have now examined the efficacy of ACT treatment in single femoral condyle cartilage lesions, and we have also examined ACT treatment with combination of ACL insufficiency and also 10 percent preliminary data on

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osteochondritis dissecans treated with ACT.

[Slide.]

The methods of clinical evaluation in this second follow-up has been Modified Cincinnati rating system of knee function, the Lysholm score, which is a Swedish score of function of the knee, visual analogue scale including certain subjective functional parameters of the knee rated zero to 10.

Tegner Wallgren's activity score, other clinical rating, and clinical rating from poor to excellent according to the New England Journal of Medicine article. The baseline measurements were established by retrospective short review and questionnaires.

[Slide.]

The results on the femoral condyle single lesion includes 24 patients, 20 on the medial femoral condyle, 4 on the lateral. Average follow-up time 4.1 years, average age at surgery 32.4 years, average size of defect 4.0 square centimeters, and the largest 12 square centimeters. In 12 patients, there were 23 previous surgeries to the actual ACT.

[Slide.]

Here are the results from the overall clinical rating, started from a pre-op pool, conditioned, and ended

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up a good result. The Lysholm score showed an improvement from 40 points before up to over 80 postoperatively. The Cincinnati rating also showed the same improvement, and the visual analogue scale, which reads at the lowest is the best, showed a reduction from 80 to below 20.

[Slide.]

On the femoral condyle and a combination with ACL reconstruction at the same time as the autologous chondrocyte implantation, the average follow-up was 3.8 years in 16 patients, average age was 26.4 years, average size 3.4 square centimeters with the largest 14 square centimeters. In 15 patients there were 31 previous surgeries in this group.

[Slide.]

Here are the results. Preoperative fair result ended up in good result with a clinical rating overall in the Lysholm score showed a significant increase. All p values up on the left showed a significant increase.

The clinical rating also showed a significant increase from 35 before to about 60 after. The visual analogue scale shows a reduction of symptoms to about 30 on the 120 scale.

The femoral condyle with the diagnosis of osteochondritis dissecans included 19 patients, average

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follow-up 3.1 years, average age 26.8 years, average size 4.3 square centimeters, and the largest area transplanted 16 square centimeters. The bony defect was not treated with bone graft, just filling with autologous chondrocytes.

In 15 patients, there were 45 previous surgeries in this group, and the results show a great improvement in the overall clinical rating. In the Lysholm score, significant improvement, as well as in the Modified Cincinnati rating, and visual analogue scale showed significant reduction of symptoms.

[Slide.]

The clinical outcome, if you look at the New England Journal of Medicine rating were excellent no symptoms, good, only symptoms on strenuous activity with pain, you see that femoral condyle single, 16 had an excellent and 7 had a good result.

With the ACL combined with cruciate ligamentous construction, you see of 16 patients, 8 had an excellent, 4 had a good result, 2 fair, and 2 poor. An OCD from 19 patients, 14 had an excellent, 3 had a good result, and 2 had a poor result.

I will return to patella.

[Slide.]

The clinical outcome two to nine years after

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autologous chondrocyte transplantation shows good or excellent results in isolated femoral condyle of 90 percent, in OCD close to 90 percent, and the combination, ACL reconstruction and autologous chondrocyte transplantation 75 percent.

[Slide.]

The patients' self-assessment whether they were improved by the study or not shows that almost 90 percent considered improved in single lesions, FC and ACL combination 75 percent, and OCD almost 90 percent.

[Slide.]

The patella results may have some special attention. In the first paper, we only had 7 patients with patella transplant. One had an excellent and one had a good result, three had a fair and two poor.

If you assess the following patient after this article, you have five excellent results, 6 good results, and 3 fair results. So I think there is an improvement by better technique and by better analysis, and reconstruction of malalignment and patella instability.

[Slide.]

So the patella factor associated in improved results may be due to better technique where you analyze the background factors and correct them with the proper

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alignment. You have to do a wide excision of the damaged cartilage to secure a healing, and you have to have a well-controlled rehabilitation program.

With these improvements, we think that we can reach in the future better results even on the patella.

[Slide.]

So, in conclusion, autologous chondrocyte transplantation in our opinion is indicated in treatment of single femoral condyle lesions, femoral condyle lesions combined with ACL reconstruction, and osteochondritis dissecans on the femoral condyle demonstrated by improvements in clinical rating, Lysholm score, Modified Cincinnati score, visual analogue scale, and patient's own evaluation of improvement.

52 of 59 patients, 88 percent, were rated good to excellent at three years and 11 months follow-up.

Thank you.

DR. HANLEY: Doctor, before you leave, could you state your affiliation with the sponsor?

DR. PETERSON: Yes. I have had my trip paid and hotel room, and I have been acting as a consultant. We have a research grant to the University of Goteborg to be able to do basic and clinical research.

DR. HANLEY: Thank you.

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DR. FREAS: Dr. Hanley, by oversight, I forgot to ask the previous speaker his affiliation with the sponsor, and at the end of this session, could he come back to the microphone and address his relationship to the sponsor.

Our next speaker is Dr. Anders Lyndahl, Associate Professor, Goteborg University.

DR. LYNDAHL: Mr. Chairman, my relationship with Genzyme, I have a sponsor research agreement, I am a consultant, and Genzyme paid for my trip. I would like to thank the committee for the opportunity to present recent data regarding chondrocyte implantation.

I myself have been working together with Dr. Peterson since the mid-eighties, and I have a 10-year experience in autologous chondrocyte transplantation from my laboratory and I have a five minute speech.

I would like to present biochemical and mechanical evaluation of repair tissue after autologous chondrocyte transplantation, and this is data that is not in the BLA application, it is additional data.

[Slide.]

I think it is important when we discuss the different therapies that it is not so strange to use autologous chondrocyte transplantation since all other therapies actually is a cell therapy. Either you recruit

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cells from the bone marrow or you transplant the cells by culturing them first and then implanting them.

[Slide.]

I also think it is important to distinguish the two entities of regenerating tissue and repairing tissue, and I think that repairing cartilage tissue means that you replace the tissue with new cells and matrix, not necessarily the original type to distinguish from regenerated cartilage, which means that you actually replace the tissue totally to the same original structure, and I think that we are working with today different repair tissue where autologous chondrocyte transplantation is one type.

[Slide.]

I would like to compare the different tissues. If you look at the left panel, it is normal hyaline cartilage taken from the biopsied area of one of the patients. The middle is one of the regenerated area by autologous chondrocyte transplantation, and the right one is the repair tissue also generated by transplantation of fibrous type.

If you look at polarized light, you are able to see the difference between the normal hyaline at the fibrous tissue, but there is also similarity in the polarized light for the regenerated repair tissue.

[Slide.]

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I will now provide the histological data showing evidence for repair tissue with hyaline-like cartilage properties following autologous chondrocyte transplantation and the correlation of clinical outcome with indentation of graft area and histological data.

[Slide.]

There are 30 patients that underwent second-look arthroscopies and 11 consented to arthroscopy indentation tests and biopsy, we also did histochemical analysis by Type I and Type II -- Type X is not yet available -- collagen aggrecan and histochemistry and we also did an independent blind evaluation of histology by three independent individuals.

[Slide.]

This is just data that is focused on the femoral condyle, which is the current indication for the autologous chondrocyte transplantation procedure, and you see a correlation between the hyaline-like tissue and the good and excellent result, and the fibrous tissue and poor and fair result, but there is also fibrous repair tissue with a good to excellent outcome.

[Slide.]

This is immunochemistry of just an example of collagen to an aggrecan in one of the repair tissues, and in

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the total of 22 biopsies analyzed, the staining pattern is indicated by minus 2, 3-plus, and if you look at the left panel with normal hyaline cartilage, it stains both for the Type II collagen, aggrecan, and very little for Type I, and the hyaline repair cartilage has similar staining pattern although a little less in intensity while the repaired fibrous cartilage has no staining for Type II collagen.

[Slide.]

We also did collaborative work with Dr. Kiwiranta from Finland and used an indentation instrument, which measures stiffness to indentation.

[Slide.]

This represents results from 11 patients where we had looked at 12 different transplantation sites and the stiffness to indentation, and if you compare the repair tissue with the hyaline character, there is no difference in indentation force to the control tissue in the same knee, and it was compared to the contralateral knee.

However, if you have the fibrous repair tissue, there is a marked difference between the indentation force compared to the hyaline repair tissue. The normal healthy cartilage has a range between 2.5 to 7.3 newton with this instrument.

[Slide.]

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In conclusion, autologous chondrocyte transplantation is capable of generating a hyaline-like cartilage and we have about 80 percent of the patients that we looked at that resulted in hyaline-like cartilage, and we are not able to get that type of tissue with the current treatment procedures, and there is a positive correlation between histology and mechanical properties in clinical outcome with patients treated with autologous chondrocyte transplantation.

Thank you very much.

DR. FREAS: Thank you.

DR. GILLOGLY: I am Scott Gillogly. I spoke two speakers ago. I am a consultant with Genzyme Repair. My expenses were paid for this visit today.

DR. FREAS: Mr. Chairman, that is all the people that responded to the Federal Register notice asking to speak this morning. However, in addition to the speakers, I have received the following letters from patients requesting that I read their letters into the public record. Apparently, they have never heard me read before.

Due to the time constraints and the number of requests, we have furnished each committee member in their blue folder in front of their desks the letters that we have received. These letters will be made part of the meeting

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documents and will be available under Freedom of Information Act.

There is a limited number of copies of these letters available on request at the desk outside in the hallway. For the purposes of the record, the letters were received from Dr. James Garrick, Dr. William Mitchell, Dr. Melvin Deese, Mrs. Juliana Futardo, Dr. Ralph Venuto, Dr. Michael Drucker, Dr. Gregory Bigler, Dr. Joseph Williams, Dr. Edward Campbell, Dr. Ray Fambrough, Dr. Robert Fumich, Dr. Per Freitag, Dr. David Menche, Dr. Robert Meislin, Dr. Arnold Scheller, Dr. Arthur Ting, Dr. Jerry Cochran.

All 17 of these letters were supportive of the use of Carticel. They were either from physicians or patients familiar with the product.

Dr. Hanley, I will turn the microphone over to you.

DR. HANLEY: Is there anyone else wishing to address the panel at this time?

[No response.]

If not, we will proceed with the open session of the meeting at this time. Our first speaker in this session is Mary Pendergast, Deputy Commissioner and senior adviser to the Commissioner. She will speak on the introduction and background information pertinent to the subject under

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discussion.

DR. MILLER: I had a question about the review of those letters. Did they enumerate any statistical information other than just being in favor of, or did they say things like I had 20 patients and 19 of them were successful, et cetera?

DR. FREAS: The letters are in your packet. Many of them discuss their treatment of the patients, and I did not summarize them, no. Most of these letters were received in the last day or so.

OPEN COMMITTEE DISCUSSION

CBER DISCUSSION OF CARTICEL (AUTOLOGOUS CHONDROCYTES MANIPULATED EX VIVO FOR THE STRUCTURAL REPAIR OF CLINICALLY SIGNIFICANT ARTICULAR CARTILAGE DEFECTS IN THE KNEE (GENZYME CORPORATION)

Introduction and Background Information

Introduction and Welcome

MS. PENDERGAST: Thank you.

Good morning, Dr. Hanley, other members of our advisory committee, Dr. Friedman, Dr. Siegel, and Dr. Zoon, and to all of our audience today.

I am pleased to be able to address you this morning. We are here today to discuss a particular product

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Carticel made by a particular company Genzyme Tissue Repair, but the work that you do here today fits into a much broader framework and how the Food and Drug Administration has considered and will consider in the future all cellular and tissue related products from conventional banked human tissue, reproductive tissues for infertility, as well as the most sophisticated cellular and gene therapies.

I would like to briefly discuss where we have been and where we are going in these fields of explosive growth. In cases of new types of biologic technology, historically, FDA often waited until the company's product was very mature and then asked itself how should we regulate it.

Sometimes the company's expectations of what we might do matched what we would decide upon, but sometimes the company's guess as to how we might react were off the mark. If the company guessed wrong, the development of the product might not match FDA's expectations and the company would have to go back and start over in their clinical trial development.

In other cases, such as this one, FDA first decided it would not regulate Carticel, but then we reconsidered and advised Genzyme that their product would be regulated.

Historically, FDA also tended to regulate cellular

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and tissue related products through regulatory controls which were product-specific. This chart represents the decisional process that we tried to go through, but even this elaborate diagram could not fairly describe all the ins and outs of our regulatory schemes.

Our regulatory schemes were like a patchwork quilt. Some products were regulated stringently while other products are not regulated at all even when they presented some of the same public health concerns as the regulated products.

For example, some allogeneic tissues taken from one person and given to another were tested for infectious diseases while others were not. Modern technologies have led to a proliferation of novel products that cross territorial boundaries, and because cellular and tissue related products were considered in two different centers at the agency, we also ran the risk of applying inconsistent standards.

To solve these difficult issues, we are working hard to reinvent our regulatory framework for all cells and tissues that will protect the public health while fostering innovation and patient care.

To solve company's concerns that they did not know in advance how we might regulate them, we will explain our

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regulatory requirements in advance. We have created a conceptual scheme that will permit innovators to understand what they have to do to meet FDA standards before they begin their first study, so they can make rational decisions about whether they want to invest in the new technology.

To solve the patchwork quilt of regulation, we are replacing the numerous separate product-specific regulatory schemes with a unitary system, so that all cellular and tissue related therapies will be regulated according to the risks they present to patients and to the public health.

The range of products covered is far too broad to allow either a case-by-case or product class set of requirements, so rather than focus on the particular tissue or cell, we will focus on several fundamental principles, and we will increase regulatory requirements incrementally as the risks of the products increase, and to alleviate any inconsistencies in approach between our two centers, we have created a tissue related group, three highly qualified scientists from our Center for Biologics and three from our Center for Devices.

These six scientists will work together to make sure that our conceptual approaches and demands remain consistent across the agency, and as today quite clearly shows, having our Center for Biologics come to a Center for

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Devices Advisory Committee is another way in which we can and will draw upon relevant expertise and experience.

Now, let me very briefly describe our new framework. This second chart shows that we are replacing our diagram with a conceptual approach that focuses on five areas of product concern.

We ask ourselves: (a) does the issue pose a risk of transmitting infectious diseases, such as hepatitis, AIDS, gonorrhoea; (b) what kinds of handling and processing controls would be necessary; (c) does the product need FDA approval for safety and effectiveness; (d) what regulation is needed for product labeling and advertising; and (e) do we know who is doing what, how can we educate the industry.

For each of these five areas of concern, we will ask ourselves three questions: what the important product characteristics, what should industry do, and what should industry submit to the FDA.

This third chart shows the product characteristics that are of concern to us. Thus, for example, it is hard to read, but the first line says autologous versus allogeneic versus family-related allogeneic. Thus, for example, the infectious disease concerns are greater for allogeneic tissues than for autologous tissues.

The next line reads viable or non-viable.

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Infectious disease issues are greater for viable tissues than for non-viable tissues because viable tissues transmit more diseases than non-viable tissues.

For processing concerns, our principal concern is whether the tissue will be minimally manipulated or more than minimally manipulated. If it is minimally manipulated only what we call good tissue practices will be required. If it more than minimally manipulated, a higher level of control of processing will be expected.

For safety and effectiveness concerns, if a product is used for its natural function, its homologous function, then, we will have fewer concerns than if it is being used for a function not found in nature, and if a product is for a structural or local use, it will raise fewer concerns than if it is for a metabolic use that will have repercussions throughout the patient's body.

All claims will have to be truthful and not misleading, and all companies will have to register with the FDA and tell us what products they make.

Using this flexible tiered approach, the FDA will limit its regulatory concerns to the issues that matter most to the public health, and over time, as technologies mature, FDA will be able to relax our regulation of them.

For example, we used to think that cell separation

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was more than minimal manipulation. We are now comfortable that it doesn't change the biological characteristics of the cells, so we now consider it minimal manipulation, thereby decreasing the amount of regulatory control necessary.

Yet at the same time the plan is sufficiently broad and flexible that it will be able to accommodate new technologies that we can only dream of today. I will not explain our new regulatory framework in further detail today.

A description of the new framework can be found in our Reinvention of Government report and in a companion piece that should be available on the table outside the room, and you are all invited to discuss this with us in open public meeting on March 17th, but I have taken the time to explain a little bit about where we are headed in order to give you a context for our work today or for your work today.

The Carticel autologous cellular product that will be considered today has been central to FDA's tissue framework. Over a year and a half ago, when Genzyme Tissue Repair began marketing their product, the types of clinical studies and clinical endpoints that might be needed for approval had not been established or articulated.

We also found that the advice we have been giving

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industry was not totally consistent, so we had to determine an approach to Carticel and other similar products.

Preliminary evaluation of the Carticel processing procedures by FDA suggested that the production was of sufficiently high quality to assure product safety, so Genzyme was allowed to continue to market their product while FDA held several public meetings and a Part 15 hearing to better formulate our policy.

We then created a manipulated autologous structural cell policy which Dr. Siegel will describe to you in greater detail. Under our new approach, Carticel would also require premarket approval because it is more than minimal manipulation, but our new framework will only govern in the future.

The evaluation of the clinical data presented today needs to be flexible and balanced by the fact that no formal clinical study requirements existed at the time Carticel was developed. Regulation in a period of change is always especially challenging.

As the rules change and as technologies are regulated for the first time, we will be confronted more and more with the situation we have here today where a product that was not regulated becomes regulated after much of the product development work was done, however, we must accept

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the fact that we will have many firsts as we try to fill in our patchwork quilt of regulation and change it into a seamless whole.

We recognize that it is especially difficult to balance the need for knowledge with a sense of fairness in these situations. This advisory committee's practical clinical experience will be particularly helpful to us as you go forward in your deliberations today.

So, thank you very much for your assistance and your willingness to help us out.

DR. HANLEY: Thank you.

Our next speaker will be Dr. Jay Siegel, Director of the Office of Therapeutic Research and Review.

Overview on FDA Policy

DR. SIEGEL: Mr. Chairman, committee, and guests, it is indeed a pleasure and an honor to be here today.

[Slide.]

As you have heard, there are many aspects of the product we are considering today and the policies that have been under development that are pertinent to it, that are quite novel. So I would like to spend a few minutes at this point of time reviewing a little bit of relevant issues regarding policies pertinent to this application and a bit of the history behind them, although you have already heard

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said most of what I was going to say in that regard.

[Slide.]

In October of 1993, after several years of dealing with various somatic cell therapies including gene therapy through genetically modified somatic cells, the Center for Biologics at the FDA issued a Notice describing our intended application of current statutory authorities to this class of products.

That Notice said that cells subject to licensure as final biological products and intended for use as somatic cell therapy include cells manipulated in a way that changes the biological characteristics of the population, for example, by expansion, selection, encapsulation, activation or genetic modification.

We at the Center for Biologics and our colleagues at the time, the Center for Devices, were incompletely aware of the extent of overlapping jurisdiction and interest that the two centers had in these products and that, in fact, there were numerous products being regulated in both centers.

So while this message came out from the Center for Biologics, our Center for Devices had indicated to Genzyme that Carticel was, in fact, an unregulated device not requiring clinical evidence of safety and efficacy

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submission to the Agency prior to marketing.

So the project, as you heard, was marketed. The Center for Biologics learned about this, some inquiries and discussions began with the company and as well with the public in a Part 15 hearing with industry in general to determine the appropriate jurisdiction and the appropriate regulatory approach.

Ultimately, this led in May of last year to the issuance of a guidance to industry regarding manipulated autologous cells for structural repair or reconstitution, the class of products of which Carticel cell therapy is a member and which we now sometimes refer to as MAS cells.

[Slide.]

In this guidance document, we clarify that this product class would be subject to licensure as a biologic, that we would phase in that policy requiring either IND exemption or marketing approval by no later than November of 1997, and indicated, as noted by Mary Pendergast, a willingness to work flexibly with industry and manufacturers to ensure that one would minimize disruption of product development and clinical availability as the regulatory environment was evolving.

This guidance document has a section on clinical data requirements for premarketing approval which notes a

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number of things, and I am going to quote directly from the document which was provided to the members of the advisory committee with their briefing packages.

It noted that the Agency recognizes that a flexible approach for clinical investigations of MAS cell products may be feasible because of certain attributes of structural defects and of MAS cell therapies.

These include (a) the likely persistence of many structural defects when left untreated; (b) the possibility of short-term benefits together with the need to assess long-term safety and efficacy; (c) the frequent availability of imaging or biopsy evidence of structural repair with high likelihood of predicting clinical benefit; and (d) low probability of systemic toxicities.

Based on these determinations, a number of statements regarding regulatory approach, a number of guidances were offered. First, the use of short-term, one year or less, endpoints directly measuring clinical benefit, it was noted, may be sufficient evidence of efficacy to support approval if a favorable risk-benefit evaluation has been established and if long-term safety concerns are low. The Agency noted there that longer term outcomes could be addressed in a post-approval phase were those conditions met and approval given.

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Evidence of normal or repaired structure may be accepted as evidence of efficacy where there is a high probability that it will be associated with clinical benefit.

The Agency has a lot of experience with surrogates for outcome measures, some of which have proven to be quite useful, others have been surprisingly misleading, for example, some of you may be aware that certain anti-arrhythmics in the post-myocardial infarction area, although they suppress ventricular premature beats, seem, in fact, to increase rather than decrease the likelihood of mortality.

It was generally felt, though, that in some of these cases, there would be a high probability that there are certain things perhaps that you might see -- now I am speaking in general terms, I am not trying to judge whether that is met in the current case or not -- there are certain aspects where you could look at a structure, say, skin after a burn, and see that it looked quite normal or repair to a normal or near normal condition where you might have a very high probability of assurance that that was clinical benefit without having to measure, say, infection or other outcomes that are more directly translatable into clinical benefit.

Extensive screening by laboratory or physical

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examination of large numbers of patients for systemic toxicity generally will not be required in the premarketing phase for MAS cell products.

I am sure the committee is probably used to this approach in terms of many devices, typically for drugs and biologics -- and this is being considered a biologic -- one needs to get a broad spectrum of, say, liver, kidney, other physiological measurements in large numbers of patients to ensure adequate safety, for these largely local therapies it was indicated that is not necessarily always the case.

Therapies using manipulated autologous cells for structural repair need not be demonstrated to be superior to other existing therapies. This is true of most, but not all, drugs and biologics facing approval at the Agency. Just for clarity, they need to be proven effective.

The way to prove a drug effective is most commonly by superiority to placebo or no-treatment control, sometimes by showing equivalence to an effective treatment if the efficacy of that treatment is well established and well quantifiable, but in any case, it is not true in most cases and is not true for this product class that a new therapy needs to be better than what else is out there. It needs to be effective, it need not be more effective.

It was noted that MAS cell products for serious or

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life-threatening conditions may demonstrate efficacy under accelerated approval regulations using surrogate markers for clinical benefit. In these cases, more definitive proof of clinical benefit should be generated in post-marketing studies, and I will summarize those regulations briefly in a minute.

Additionally, it was noted that while prospective randomized controlled clinical studies traditionally have been the best way to demonstrate safety and efficacy, however, where studies of MAS cells without internal patient controls provide evidence of effective structural repair which clearly represents improvements in outcomes compared to patients in an appropriate historical database, this may be sufficient to demonstrate efficacy.

[Slide.]

Now, the accelerated approval regulations which occur in Code of Federal Regulations, Section 601, Subpart E for biologics, state that the regulation applies to biologics that have been studied for their safety and effectiveness in treating serious and life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments.

So for this particular regulation, the standard is a little different from what I discussed in general for

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approval. Accelerated approval of regulations applies to those products that offer something new and different, not simply to a "me too" drug or biological.

The Agency does believe, however, that in discussing I know application of this regulation under the ecology initiative, the Agency does believe that a new therapy need not necessarily be better than other experimental therapies that people are interested in and excited about. It need be an improvement over standard and accepted and proven and, in the case of therapies that are drugs or biologics of approved therapies that exist.

The policy on accelerated approval goes on to say -- and this is the heart of the policy -- that the FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely based on epidemiological, therapeutic, pathophysiological or other evidence to predict clinical benefit.

So this policy represents a codification of FDA approaches to when and how one might accept rather than a direct evidence on survival or on serious irreversible morbidity one may affect an alternative measurement. Most commonly used has been CD4 counts in HIV, we have used tumor

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size in cancer, for drug approvals to allow marketing at an earlier phase of product development.

I say "an earlier phase of product development" because the regulation goes on to support the concept that it is critical that product development not stop at the point of accelerated approval.

[Slide.]

In fact, it states that approval under this section will be subject to the requirement that the applicant study the biologic product further to verify and describe its clinical benefit where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit.

[Slide.]

It allows that the FDA may withdraw approval if a post-marketing clinical study fails to verify clinical benefit or if the applicant fails to perform the required post-marketing study with due diligence.

[Slide.]

I would like to discuss a little bit about control treatment and about historical controls. Just for clarity, the reason I am talking about historical controls and its relevance to this case is that, at least in our view, the data you will be looking at represent

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historically-controlled data.

It is true that there are comparisons being made here within the clinical trial from patients at the end of treatment to their condition at baseline, and those comparisons can certainly be very informative, however, it is of note that those comparisons test the hypothesis as to whether there is change in the patient from baseline. They do not test a null hypothesis of whether there is a drug effect.

Whenever a change is observed from baseline, one explicitly or implicitly compares that change in baseline to a change in patients who receive the different treatment or no treatment, if that is within the study, if it is randomized, that would be a randomized trial with baseline comparisons.

In other cases where those patients are not in the trial, one makes such comparisons either on the basis of identifying explicitly a control group or by experience or literature review in a more implicit comparison which sometimes can be successfully done, most commonly when a disease has a very reproducible and predictable condition. For many tumors, for example, spontaneous shrinkings of the tumor is very unlikely.

One doesn't need to include a control population

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untreated to see if their tumor is going to shrink. If one observes it with a drug, one can reasonably presume that that is a drug effect, not a spontaneous effect.

It is important to note that historical control trials, while they have their limitations, are accepted by FDA regulations as one type of adequate and well-controlled trial when done appropriately.

The limitations are, and the chief concern, is comparability of the patients to the patients to whom they are being compared. Because there is lack of randomization, there is concern about the baseline status of the patients - do they have the same prognostic factors, the same extent and severity of disease, and because there is lack of blinding there is concern about comparability in terms of ancillary care and management, patient expectations, evaluator expectations, and so on.

Nonetheless, these issues can be addressed, if not as rigorously as they can be in the presence of randomization and blinding, and every attempt has been made to do so.

There is a lot of talk in international negotiations about the utility of historical controlled trials. These negotiations are in the early stages, this is not a draft agreement. This is part of the International

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Conference on Harmonization.

There are documents -- in fact, I am just back from Tokyo yesterday, discussing these documents regarding the use of historical control groups, which note -- again, this doesn't necessarily represent international agreement, but it certainly does reflect a widespread FDA feeling that historical controls are most useful when the course of a condition is predictable, so that is when the course without the therapy under consideration is fairly high, easy to predict, is uniform or nearly uniform, when the course on the study therapy is markedly different, sufficiently different that one can relatively easily make determinations as to whether differences were due to the drug or might have been due to more subtle differences in the patient populations and how they were managed; when the endpoints are objective, objectively measurable endpoints are less subject to bias, bias in the sense of inaccurate measurements or measurements that don't reflect drug effect than are subjective endpoints; when the covariates, when the predictive or prognostic factors which influence outcome are well characterized, and when the control group, the historical or external control group is well characterized and closely resembles the study group.

Also, in current drafts of the document

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interestingly is a statement that seems relevant to the case at hand, it says it is inevitable, however, after talking about how to plan an external control group for historical controls -- actually, I can read that part -- it says, "Use of an external control group should be carefully planned and considered with a clear prospective definition of the control group and a serious attempt to define the treated and controlled population and study endpoints."

It is inevitable, however, that sometimes a single group study not intended to be an externally controlled trial supporting effectiveness will provide results so dramatic that a retrospective attempt to derive a control will be forced upon the investigator.

When this happens, an attempt should be made to examine a variety of historical experiences choosing the one whose patients' treatments other than the study drug and assessments most closely resemble those of the current study group, and if possible, choosing the group prior to assessing outcomes.

[Slide.]

So, to summarize, the notion regarding control treatments in a study such as this -- to raise my final slide and additionally, I guess, to introduce another point or two -- optimally, one should compare patients receiving

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the study article -- which certainly is operant in this case, although it is written to generalize -- to patients treated identically except for the study article.

Sometimes in historical studies, that is impossible because those patients don't exist and sometimes even with the best of planning it is impossible because study treatments are often administered -- in this case with surgical procedures -- are often administered with many concomitant procedures which are not necessarily done the same way in the absence of the study drug, so this represents an ideal that best facilitates the ability to distinguish effects that are due to the study article versus effects that might be due to other factors.

However, when treatments in addition to the study article vary, a reality which sometimes occurs, we believe that a determination should be made -- and when that treatment shows effects -- we believe a determination should be made that it is likely that the study article contributed to the observed efficacy.

We feel that in such a case, a commitment for post-approval confirmation of the contribution of the approved biological to the observed efficacy may be required.

This has been addressed in the abstract,

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potentially in the real setting in some parts of the Agency, in situations, for example, where two experimental agents are combined and show an important effect on a serious disease, it may optimally in drug development one ought to be able to determine and do the appropriate clinical studies to know exactly which of those therapies or agents contributes to efficacy, and we certainly attempt to do development in such a way. There may arise cases, however, where it is highly likely, but not certain, that one did contribute. The Agency does believe in such a setting that we have the ability to approve an agent on that basis requiring post-approval.

So, this is a broad variety of regulatory documents and regulatory approaches. Some undoubtedly will be applicable to the discussions today, some will not be depending in part on your scientific feeling as to which standards are or are not met, but I hope that this gives a little bit of background of some of the regulations, guidances, and whatever, that the Agency has produced pertinent to these policies, and I will be available through the course of the day to answer questions about them as needed.

Thank you.

DR. HANLEY: Thank you.

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Do we have any questions from the panel for Dr. Siegel now concerning any of the issues he has brought up?

[No response.]

DR. HANLEY: Thank you.

Our next speaker in this session will be Dr. Robin Poole. He is Director of Joint Diseases Laboratory at the Shriners Hospital for Crippled Children in Montreal. He will give us an overview of cartilage in the knee joint.

Overview on Cartilage and Knee

DR. POOLE: Thank you, Dr. Hanley, ladies and gentlemen. I have been working in cartilage for over 35 years and I look at it almost every day of my working life, so I am looking at cartilage today with you, so I can perhaps present to you a background to the discussions, so we can provide a setting for these discussions, and I will try and ensure that we understand what we are talking about.

Because of time I am going to keep my comments to a minimum. It would seem that the carousel is having problems sitting on the projector.

[Slide.]

The tissue that we are talking about, articular cartilage particularly of the knee joint, is a tissue which covers the ends of the bones, which would otherwise be rubbing together to create tremendous pain and destruction.

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This tissue, as you can see here, is an incredibly important tissue because with the synovial fluid it provides an almost frictionless articulation. We are looking at an inter-phalangeal joint here. This frictionless articulation is essential to the function of the joint to joint articulation.

[Slide.]

If we look at that cartilage in the knee opened at autopsy, you can see it's a white, glistening tissue, and it covers the whole of the surface of the femoral head. These are the condyles, and this is the intercondylar notch, and these are the anterior and cruciate ligaments here. The tibial plateau is a little hidden, and these condyles are articulating, particularly parts of them, with respect to the tibia and with respect to the meniscus, which we will come to in a moment. So this tissue is essential for the frictionless articulation.

[Slide.]

If we look at the structure of the joint, here we have two bones forming what we call a diarthrodial joint, and this joint is enclosed by a capsule lined by a synovial lining layer. This synovial lining layer serves to keep the joint healthy, free of infection, and also to provide a special type of synovial fluid containing lubricants, such

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as hyaluronic acid, that provides an almost frictionless articulation with that hyaline cartilage.

So the joint is an organ, and the functioning of this joint is very much dependent upon the component tissues, and within the knee we have the menisci, as we have shown here, which provides an interface within this articulation, and they also serve to stabilize this articulation within the knee.

If anything happens to any cartilage within the knee or within a ligament or to the meniscus, creating instability or change in articulation, in the vast majority of cases that leads to an accelerated progressive degeneration of the hyaline cartilage covering these bones, which leads to the development of clinical osteoarthritis, so the integrity of the knee is extremely important.

[Slide.]

Here we can see the menisci looking down upon them. These are the tibial plateaus here. So it is a very composite articulation, and this articulation is with the femoral condyles that I just showed you.

[Slide.]

If we look at a knee on X-ray, one sees a space between the femur and the tibia, and this space is created by the presence of that articular cartilage. When that

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articular cartilage is destroyed in a disease like osteoarthritis, we have a loss of joint space, and that is a consequence of loss of articular cartilage, and that leads to the loss of joint function, considerable pain and destruction.

As I said, if there is injury to the articular cartilage, it can accelerate this process, therefore, it can develop in individuals where it might otherwise not develop.

[Slide.]

This is what the articular cartilage looks like if we stain it with Dr. Rosenberg's stain safranin O and fast green. The safranin stains the molecules called proteoglycans, which as we will see in a moment are a very important part of the cartilage.

This is the articular surface. That is where the actual articulation takes place, and this is an example taken from a femoral condyle. You cannot see the subchondral bone here.

[Slide.]

If we actually look at a diagrammatic of this, this is the articular surface. This is the subchondral bone. This is a partly calcified interface. This is deeper cartilage, more intermediate cartilage in the superficial zone, and this superficial zone is incredibly important. It

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is absolutely essential that this zone stays intact, because when it starts to degenerate, that is the beginning of the end. That is when the cartilage starts to break up progressively.

[Slide.]

If we look at the primary composition of the cartilage, in the adult human articular cartilage there are very few cells, just about 2 percent of the volume, compared with probably 10 times that concentration in the newborn, and this is a big problem, because this cartilage is not vascularized.

So when it is injured, it is not possible to bring in blood vessels, to bring in stem cells to repair the cartilage, such as would occur in a soft connective tissue or even in bone, so this lack of vascularization is a big problem.

In the child, where there are many cells and there is much turnover of matrix and there is much less in the adult, there is significant capacity for repair, and we see this in juvenile rheumatoid arthritis, for example, but we don't see that capacity for repair, natural repair in the adult.

There is a lot of water there, and this water is bound to the proteoglycan called proteoglycan aggrecan, as

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well as some of it to the collagen, Type II collagen, and about 15 to 25 percent of that matrix is made up of collagen, and this is a special type of collagen as you will see in a moment.

It is called Type II collagen. We find it only in cartilage and in the vitreous of the eye, whereas, in soft connective tissues like skin and bone, we find a different collagen called Type I collagen. The Type II collagen is critical for the function of the cartilage as I will describe in a moment.

[Slide.]

The articular surface is organized into what we call collagen fibrils, and these provide the tissue with its tensile strength, its tensile properties. It makes it a strong, tough tissue, just as the fibrillar collagens in skin and bone, for example, and ligaments and tendons, make those tissues tough and strong.

At the articular surface, the fibrils are very thin and arranged parallel to the surface, whereas, deeper down they are thicker and organized in a more random fashion, but this articular surface, organization is very important as you will see in a moment.

[Slide.]

This is just to show you that the collagen content

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actually relates to the tensile properties of this human articular cartilage. Data from the work of Kempson in the late sixties, early seventies.

When the cartilage is degenerative, as shown by these yellow dots, experimental points, the collagen may still be there, but it has lost its tensile properties frequently, such as in osteoarthritis as you can see here.

[Slide.]

This is the articular surface measured for its tensile property by Kempson, and this is the deep zone of the cartilage. The tensile properties are most pronounced in the articular surface. When there is very early degeneration within cartilage, those tensile properties are lost, as shown by the red columns compared with the blue. This is an adjacent normal-looking area, so there is tremendous loss of tensile properties. That is early osteoarthritis. That is a progressive degenerative process that can't be reversed.

[Slide.]

If we look at the structure articular cartilage, the tensile properties are endowed by these collagen fibrils, these rodlike structures. This is like the steel in reinforced concrete.

The proteoglycans are mainly the large

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proteoglycan aggrecan, as shown here, and they can bind up to 50 times their weight of water. These are the molecules that give the cartilage its compressive stiffness, its capacity to recover rapidly from compression from indentation. They make it stiff and indentation is reversible, and when the tissue starts to degenerate, those molecules start to be destroyed and lost, and you lose this capacity to resist mechanical load.

The collagen fibrils become exposed to further mechanical stress. They also become exposed to proteases that destroy not only the proteoglycan, but the collagen fibrils, and the protease is primarily produced by the chondrocytes, as we now know.

That collagen is Type II collagen, and to hold these proteoglycans in the matrix you need Type II collagen. If you have Type I collagen there, it is almost impossible to have this structure of a compressively stiff, tensile strong tissue.

The presence of Type II collagen is essential because somehow molecules interacting with it, such as Type IX collagen, and other molecules on the surface, seem to provide a linkage between this aggregated proteoglycan network and the collagen fibrillar network, so the presence of Type II is essential.

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In a degenerate cartilage we still have Type II collagen, and in osteoarthritis we still have Type II collagen. We have no Type I collagen in osteoarthritis in normal degeneration of cartilage.

In a fibrous repair cartilage, we will have Type I collagen present, and the amount of that Type I collagen will determine whether or not that cartilage can function. If there is too much of it, that cartilage cannot function normally and will progressively degenerate in time.

[Slide.]

So we look at the normal human articular cartilage and then we compare it with this. This is early osteoarthritis. There is splitting from the articular surface and these splits become progressive, and they eventually go to subchondral burr.

The cells, the chondrocytes start to divide and they actually make more matrix. They try and upregulate the production of matrix, but this is a one-way street, and that degenerative process continues and continues, and it is characterized therefore by fibrillation splitting of the articular surface, and it starts at the surface of the cartilage.

[Slide.]

These are the cells, as you can see, the

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chondrocytes forming what we call clones, trying to make new cartilage, but this splitting cannot be repaired. Mitchell and Shepherd showed that only if you start to pin it can you effect repair in the skeleton-mature animal, but ordinarily this is a process that we are finding very difficult to control, and we end up with this, a very degenerate tissue.

There is no Type I collagen there, it is still Type II. It has lost most of its proteoglycan and most of the collagen has been destroyed. It is still there, but it has no functional properties.

[Slide.]

It starts at the surface. This is actually staining for degeneration, denaturation of the Type II collagen. This is a young cartilage as you can see here, a young cartilage from a 41-year-old non-arthritis, and then we go down to an arthritis cartilage, and the collagen damage starts at the surface, and this is where the proteoglycan, which has been stained here, starts to disappear compared with the non-arthritis cartilage.

So what is happening at the surface is incredibly important because that damage progressively moves down through the cartilage involving eventually the whole cartilage compared with the normal cartilage which survives and there is very limited damage.

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[Slide.]

Eventually, we end up with ossification of bone and loss of cartilage here. There is some residual cartilage here in this joint.

[Slide.]

If you make a hole in cartilage, even if you go down to subchondral bone and penetrate it, and blood vessels come in, a repair tissue will form -- Dr. Coutts will tell you more about that -- but so far nobody has really been able to produce a hyaline cartilage containing a significant amount of Type II collagen. You get a nice tissue initially in the first few months, and then it becomes progressively degenerate.

Many workers have filled these defects, filled defects with chondrocytes with and without perichondrium or periosteum, because these two latter tissues contain chondroprogenitor cells or osteoprogenitor cells that produce either chondrocytes or osteoblasts. With mechanical loading, you tend to produce chondrocytes.

So the question is, is there a technology now that we can look at and determine whether or not we really fill this gap and whether or not this process is working in a way that hasn't demonstrably worked before.

[Slide.]

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This is from the work of Salter's group showing that cartilage will form, but it becomes degenerate, and then you get progressive degeneration. When you look at that, that is an osteoarthritic process we are looking at, and it will progressively degenerate.

So our concern is that if we form a new cartilage, will that survive or will it progressively degenerate in time.

[Slide.]

This is what we see in cases that have failed where there is a fibrous tissue containing Type I collagen and having none of the mechanical properties of hyaline cartilage.

[Slide.]

And if you take off the surface of the cartilage, if it is burred off, there is not a repair process that we can identify. So the cartilage ordinarily in the adult doesn't have the capacity for natural repair, and if a repair is effected, the great concern is, okay, we are repairing a defect, but in that process are we creating any damage or inducing degeneration around that defect. That is another question we have to ask, not just look at the defect, but look at the surrounding tissue, so this is an important issue to consider today.

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[Slide.]

As I said, in the immature, we get a lot of cells, and they can repair that matrix quite well it seems, but in the adult we have very few cells, so can the introduction of new cells from other sites produce a repair process?

Thank you very much indeed.

DR. HANLEY: Thank you.

Our next speaker is Dr. Richard Coutts, Director of Orthopedics at Sharp Memorial Hospital in San Diego. He will speak to us about techniques of cartilage repair.

Techniques of Cartilage Repair

DR. COUTTS: Thank you, Dr. Hanley.

It is inevitable I would guess that two speakers speaking on a similar subject are going to repeat some of the same material, but my expert friends in education say that repetition is the best way of teaching, so I am not going to apologize for any overlap that I may have with Dr. Poole. It will be brief, I assure you.

[Slide.]

We are going to be discussing the knee. I think Dr. Poole went over the anatomy of the knee quite adequately. It is a unique structure as joints go because it is dependent upon its ligaments for stability and if it loses its ligamentous support, it had a deleterious effect

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on the articular cartilage which you now understand is important in terms of how the knee is supposed to function. So the cruciate ligaments, the two on the inside of the knee, and the two ligaments on the sides, the collateral ligaments, are particularly important to the function of the knee.

[Slide.]

We see the posterior cruciate here, the anterior cruciate, the collateral. They, when operating properly, help to ensure that there will be appropriate loading of this articular cartilage, and when the loads and movements of the knee become abnormal, it has a deleterious effect on the survival of that material.

[Slide.]

Just how big of a problem are we talking about here? It has been reported that there are 500,000 procedures a year in the United States alone which identify varying severities of articular cartilage damage at the time of the procedure performance.

You have already heard that this diseased or damaged cartilage does not heal, and more than likely, particularly if the defect is in a mechanically loaded area, that this deficit will become progressive, and that the current methods, as I will show you, are somewhat

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unpredictable in their outcomes.

Dr. Poole has described to you the types of deficits that cartilage experiences. It has been reported that the early defect in cartilage degeneration is a break in the surface layer, the so-called lamina splendens, which will then progress through the body of the articular cartilage, extending potentially all the way down to the base of the cartilaginous tissue. This is a so-called partial thickness defect.

[Slide.]

These partial thickness defects do not heal, and as you have just heard, it is because it does not have a blood supply, the cells that would effect a repair are entrapped in the matrix and cannot migrate to the site of the defect. It cannot jump the distance between the fibrillar breaks in the cartilage, and consequently, it will not heal.

As I mentioned before, if this is in a mechanically quiet area, not particularly loaded, these can sit quiescently without any potential progression, but if it is in a mechanically loaded area, they tend to be progressive.

[Slide.]

The other type of defect is a so-called full

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thickness articular cartilage defect which will progress through the articular surface down into the bone. Now, this has a different pattern of repair because by breaking through the bone it gives access to the medullary blood supply to the cellular elements within the marrow of the bone, which have the potential to proliferate, to fill in the defect, and to repair it.

[Slide.]

Despite the fact that the bone marrow has cells in it known as pluripotential mesenchymal cells or stem cells which potentially could differentiate along the line of the cartilage phenotype, it doesn't seem to do so in these full thickness repairs. A fibrocartilage is what forms, and even though it may fill the defect initially, usually, by the end of a year in most animal models, this has become cicatricial, it shrinks, depresses, and fails to maintain a continuous surface for the joint.

[Slide.]

The usual process of degeneration has been illustrated very nicely by the now deceased Frank Netter, describing here the normal articular cartilage as being a nice, thick, glistening, smooth, slippery layer, and once the surface breaks down, then, there is a splitting apart of this collagenous framework, and the tissue becomes quite

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fibrillar.

It eventually breaks down and reaches to the subchondral bone, it becomes ever more progressive until such time as the subchondral bone is what is the new articulating surface, and as opposed to the cartilage, the bone has never endings, it is not smooth and slippery, it is constantly abrading off bits and particles of itself, getting into the joint and producing an inflammatory reaction and stimulating the nerve fibers in the joint itself and causing pain.

[Slide.]

What are the current methodologies, which are used for the treatment of arthritic conditions? I will very briefly summarize these. Debridement became quite popular with the advent of arthroscopy because arthroscopy by itself is procedure which has a component of debridement, because fluid is flushed through the knee joint during the course of this procedure.

This flow of fluid through the joint is removing noxious agents, cytokines probably, from the joint, and there has been a recorded benefit to patients who have arthritic conditions following arthroscopy of a varying duration.

This flushing is a form of debridement, and

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additional components of debridement, in addition to this lavage, would be the removal of loose bodies, the excision of osteophytes, the shaving off of this frondlike fibrillar cartilage, which is in the stages of degeneration, presumably removing substances which, when they break off and get into the joint, would be irritative.

This in itself will not reverse the process of degeneration, but may give temporary relief to the individual because it removes some of the offensive aspects of the degenerative process.

[Slide.]

However, in a study of patellae that had been debrided by Milgram, he found that there is nothing but a little bit of fibrocartilage on the surfaces of patellae, and there is a strong suspicion that there is a placebo effect to this aspect of debridement.

[Slide.]

From a historical perspective, interpositional types of repairs have been done. Those were, in fact, the first types of attempts to restore articular cartilage and degenerative processes dating back to the turn of the century.

A famous surgeon in Chicago by the name of Murphy had done interpositional arthroplasties of the hip joint

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with some benefit, and even today, although not as commonly, fascial arthroplasty is performed particularly in the upper extremity where pieces of fascia are removed from various parts of the body, usually the fascia lata in the thigh, and they can be interposed over the joint surfaces, and it has been reported that patients can achieve reasonable degrees of success, 80 percent with pain relief with fascial arthroplasty.

[Slide.]

The current methods for attempting to restore cartilage or to ameliorate the effects of cartilage loss fall into these basic categories here - subchondral bone penetration either by drilling, microfracturing, or abrasion, or the use of allograft transplantation of cartilage from cadavers, and osteotomy, which is a method whereby the mechanical environment in which the cartilage is operating can be altered.

[Slide.]

Let's just briefly go through these. The subchondral bone penetration techniques are designed to disrupt the bone and produce a vascular response that will, in turn, bring a fibrin clot to the region of the deficit, and that this fibrin clot will serve as the basis for a fibrocartilaginous repair, and I don't think any of the

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proponents of this methodology have claimed that anything but a fibrocartilaginous repair is going to occur.

[Slide.]

Osteochondral allografting takes tissue from a recently deceased individual, usually within 72 hours of death, with the goal of maintaining viability of the cells within the cartilage. It is believed that cartilage is an immunologically privileged material.

There is no question that chondrocytes have receptors which are not immunologically privileged, but the matrix that surrounds these cells protects the chondrocytes and keep the antibodies from reaching the cells and causing the usual immunologic response and degeneration.

There have been long-term survivals of cartilage transplantation, principally out of Toronto and in San Diego. There is a problem with logistics in using allografts. The patients have to be available on short notice when an appropriate donor is identified, and there is a limitation to the number of donors compared to the patient population that might benefit from this form of treatment. So it really will always probably remain a niche area unless some method for preserving articular cartilage is determined, so that the issues of patient need and supply can be better coordinated.

[Slide.]

Osteotomy changes the physiology and mechanics. I am speaking specifically with reference to the knee when the degenerative process has progressed to thinning of the joint space and deformity develops. There is an accentuation of the degenerative process because, as the patient stands on this now bowing knee, the loads are ever increasingly concentrated on the area of deficit.

By making a cut in the bone and changing the angulation of the tibia, it is possible to shift the weight bearing off of the degenerative portion and into the more normal aspect of the knee.

There have been some cadaver retrievals of patients who have had osteotomies, and it has been shown that, in fact, not only does it unload the area of the deficit, but it will produce or at least allow some repair, probably of a fibrocartilaginous nature, to form in some circumstances.

[Slide.]

By way of summary, the review of a large body of literature, one can say that the subchondral penetration methodologies give basically a 50 percent satisfactory outcome after a very short period of time.

It is safe to say that this method, whether it be

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abrasion, whether it be penetration of the bone by microfracturing or drilling, is highly unpredictable in its particular outcome. Some patients will do well, some will not, and some are certainly made worse.

Allografting reproduces the tissue that is missing in a very accurate fashion. There are still some problems with predictability, and the experience in the centers where this is being done shows basically that 70 percent of the patients will get a satisfactory result.

If a bipolar lesion is replaced, that would mean both sides of the joint, the results fall off very significantly, but they can be very long lasting, and probably this would be the gold standard against which any new methodology would have to be compared.

Osteotomy will give a 50 to 70 percent satisfactory outcome at 10 years.

[Slide.]

I was asked to address the issue of periosteal repair. I don't have any particular expertise in that area, but I do with a 15-year experience of studying perichondrium, which is a very similar tissue.

Perichondrium is an investing tissue that is found in certain parts of the body where cartilage exists, in this case the rib. That is a thin tissue, just like periosteum

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is, and it has the same type of stem cells present in it. Fibrous tissue, which has a cambium layer, this cambium layer contains the stem cells, which can be induced to proliferate and produce cartilage.

[Slide.]

This was one of the very first experiments that we did with perichondrium, in which the articular surface in a rabbit knee was abraded off, some holes were drilled through the condyle for attachment by the perichondrium.

[Slide.]

It is probably tough to see from the back of the room, but the perichondrium was inlaid onto this bony bed, and then harvested at various periods of time. You can clearly produce articular cartilage. This was only after seven days and in two different locations.

[Slide.]

We were quite excited by what we were able to see as a result of this type of procedure. You could grow hyaline articular cartilage which had a safranin O stain, which had the architecture of cartilage, and at the time the feeling was that you could not get articular cartilage to repair in this. It was clearly not the case as a result of this experiment.

[Slide.]

The problem was that when we started going a larger series of animals, we found that the issue of attachment predominated, and here is a piece of perichondrium that proliferate articular cartilage, but it had not attached.

Again, this probably doesn't show in the back of the room, but here is another piece that grew very nicely overlying the femoral condyle, but it did not attach. An attachment, of course, is a very critical factor in any type of cartilaginous repair.

[Slide.]

We have come up with certain requirements that we think are essential for an articular cartilage repair regardless of what methodology you use. It is a cell-based phenomenon. You cannot produce a new articular cartilage without the cells to elaborate the matrix with the exception of cartilage allografting in which the finished material is placed into the defect, one is going to require cells, and there is going to have to be a method to maintain the cells at the site of the defect.

Whether this is a patch of some type or whether it is a scaffolding synthetic material or some other type of biologic, you have to put those cells at the site of the defect and keep them there, and I think there is a third

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component, which will not be addressed today, I don't believe, and that is the role of growth factors, these very interesting proteins that have been identified which clearly influence the behavior of cells. It may take a combination of these to produce an effective repair.

But I think the good news is that the old teaching that the articular cartilage you have an adult is all you are ever going to get is clearly not the case. It is possible to produce a new articular cartilage.

Our challenge is to be able to do this predictably in a fashion where the patient is not going to be undergoing significant risk, where you can sit in the room and face the patient eye to eye and say I think you have a 90 to 95 percent chance of getting a satisfactory outcome from this procedure.

This is our goal and hopefully we will be able to make some steps forward in this today.

Thank you.

DR. HANLEY: Thank you.

We are now ready to begin with the sponsor's presentation. I would like to ask that each speaker state his or her name and affiliation to the firm before beginning the presentation.

At this time, I would also like to ask the

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committee members to hold their questions for the speakers until after both the sponsor and the FDA had had the opportunity to speak.

If you need clarification from a presenter, please feel free to ask a question, however, if it relates to material which may be covered by later presenters, please hold your questions until later.

Presentation by Genzyme Corporation

Introduction

MR. SURGENOR: Thank you. My name is Tim Surgenor and I am President of Genzyme's Tissue Repair Division, and it is my pleasure today to start off Genzyme's portion of the sessions today.

As Deputy Commissioner Pendergast has already pointed out, the review of this BLA is a very important milestone, not only for Carticel and therefore for Genzyme and for our customers, but also in the process that the FDA has undertaken to try to provide a more rational set of regulations over tissue-based products.

[Slide.]

As a result of those unusual conditions, this meeting is also somewhat unusual. This product is, as has been presented earlier, already on the market. This was developed by Genzyme between 1992 and 1994, well prior to

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the development of the MAS cell regulations.

It has been reviewed by the FDA when it was launched in 1995, and therefore there is a two-year record of performance that is available to be reviewed. Some of that information will be provided through our Patient Outcomes Registry, but there is also a record of performance in terms of the company's commitments to cell processing and data collection.

During the last two years, there have certainly been a significant increase in the amount of data that is available on both the safety and efficacy of autologous contractor implantation.

It is also true that this panel is being asked to review the first BLA that has been submitted under these guidelines, and therefore there is no precedent to guide you in the interpretation of these guidelines, and your actions will certainly have an impact on future considerations brought by other sponsors.

It is also true that one of the most interesting aspects of this review is the discussions and definition of flexibility, which we have been in discussions between Genzyme and FDA for almost two years now, and is one of the centerpieces of this new tissue regulation.

[Slide.]

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I want to just go back to from the company's point of view, the context we were in when this process and when this program was developed between 1992 and 1994. We actually have another product based on autologous cells which is called Epicel. Epicel is a keratinocyte-based skin graft which is used in severe burns and actually was introduced to the market in late 1987, ten years ago, and has been on the market ever since.

Those discussions around Epicel and other keratinocyte-based products with the Center for Devices is what led us to believe that Carticel would be an unregulated medical device.

Also, during the period 1992 and 1994 we had an opportunity to interact with a number of orthopedic surgeons and were certainly impressed with the high level of interest in having access to this innovative new therapy. There was a great deal of consensus in our discussions that there were poor expectations for the commonly used alternative therapies, and I think we would define those more as arthroscopically-based therapies for most of these younger patients.

The data that was subsequently published in the New England Journal and other data available from Sweden was very persuasive and in some cases far exceeded the amounts

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of available data for alternative therapies.

There certainly was consensus that there is a favorable risk-benefit ratio in this procedure. Again, that is one of the tenets of the FDA's regulation in this area, and also it was clear that individual surgeons own thoughts about utilization fell, in their opinion, very much in the practice of medicine as being an autologous type of tissue. Surgeons and in particular orthopedic surgeons are very used to using autologous tissues and, in fact, allogeneic tissues, and all of the other alternative procedures which can be used fall into the practice of medicine.

In response to those considerations and based on our experience with Epicel, we developed a program for Carticel which had two fundamental foundations. The first is the development of cell processing which met the most rigorous standards that we could develop, as we have now about a 10-year history in autologous cell processing and have taken elements of GMPs, elements of tissue banking standards, and developed what we believe is a state-of-the-art system for processing autologous cells.

We also developed a program around continued data collection, and we understand how important it is for there to be additional data for orthopedic surgeons to review in order to guide their use of products like Carticel.

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That commitment really was based on three sources of information: first, support of additional data collection in Sweden; second, development of an outcomes registry for Carticel; and, third, the development of comparative studies where appropriate.

[Slide.]

So, over the last two years we have seen utilization of this technology of Carticel autologous chondrocyte implantation by surgeons in the real world of medical practice. 479 U.S. surgeons have now taken patient biopsies indicating that they believe those patients are appropriate candidates for this therapy; 134 U.S. surgeons have moved on to treat patients; 223 insurance companies have approved 439 treatments, and it is important to point out as was demonstrated I think very well earlier by some of our patients, that that process is not an easy one.

The introduction of a new technology like Carticel into the medical marketplace requires a significant amount of dedication and commitment. Most importantly, from those 134 U.S. surgeons who have had to review these cases in depth with insurance companies in order to provide these treatments. So, I think just based on my conversations with many of those surgeons, these are people who, like Dr. Gillogly, believe this is a very appropriate alternative to

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what they currently have available.

We also know from our registry program that the use of the product so far has been very consistent with the labeling and with the training that the company has provided.

Now, during the last two years, there has also been a great increase in the amount of evidence for the safety and efficacy of Carticel. We have seen additional clinical data from Sweden which has been reviewed by the FDA and some of the information presented this morning which came after that review, additional histology from Sweden, our own registry program, and we also more than a year ago began developing a post-marketing study with a number of orthopedic investigators, and we are going to present that to you this morning.

[Slide.]

This is the agenda for the rest of the Genzyme portion this morning. Dr. Gary DuMoulin will present a brief overview of our processing and controls. Dr. Tom Minas will present some of his thoughts about the efficacy of alternative treatments for cartilage defects.

Dr. Moscicki from Genzyme will present and summarize the data that is in the BLA. Dr. McPherson, also from Genzyme, will present the histologic evaluation

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contained in the BLA.

We are very pleased to have two of our outside registry panelists here today, Dr. Mandelbaum and Dr. Micheli. Dr. Micheli will present the 12-month outcomes from our registry, and Dr. Moscicki will summarize and present the proposed comparative study.

The conversations and the answers to the questions that have been posed today will have an impact, obviously, on the FDA's decision about Carticel, and will begin to have impact on decisions about other products in this area.

After you review this information, we think you will be convinced that Carticel meets the criteria for approval under the guideline that has been explained to you this morning, and we think that is a very appropriate type of regulation for Carticel.

Most importantly, it preserves surgeon access to this technology, which we do think has a very favorable risk-benefit ratio. At the same time, regulation by the FDA under this MAS cell policy ensures appropriate safety by providing oversight of our processing operations, which are not covered in depth today, but which have been covered in depth in audits and other conversations, and probably most important for this group, provides a framework and a structure and a requirement for ongoing data collection and

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presentation and oversight of that data by the company.

I just want to leave you with the thought that we already have demonstrated a very significant commitment to data collection by funding a collection of data from Sweden by development of what has turned out to be a very groundbreaking registry program in the orthopedic field and by development of our own post-marketing study, all of which were done by requirements or before regulations, and we also understand that this product is not the ultimate solution for cartilage repair, and we therefore spend a great deal of time and energy and resources on continued product development in this area.

I can tell you that the feedback we have had from treatments that have actually been done and the real world experience that we are getting with Carticel on the market will be very important, have already been important, and will be important in the future to develop new technologies which make this easier and more cost effective, and we understand that that needs to continue.

That concludes my remarks this morning. I would like to introduce Dr. Gary DuMoulin, who is Director of Quality Assurance at Genzyme Tissue Repair.

Thank you.

Process and Controls

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DR. DuMOULIN: Good morning. I am Dr. Gary DuMoulin, Director of Quality Systems, Genzyme Tissue Repair.

In the absence of regulations, Genzyme Tissue Repair created a comprehensive quality assurance program based on U.S. Food and Drug Administration's Good Manufacturing Practice regulations and other guidance.

The development of ex-vivo cell therapy presents novel issues of quality assurance, however, rigorous application of well-accepted principles of quality assurance and quality control, coupled with a thorough understanding of the cell culture process, results in safe and reproducible cell therapy products.

Extensive research studies were conducted to address comparability of the autologous chondrocyte implantation process developed in Sweden to confirm and expand our understanding of chondrocyte biology, a central part of the autologous chondrocyte implantation process.

[Slide.]

Utilizing our expertise in cell biology, we have been able to demonstrate that the Carticel cell culture process is comparable to the Swedish process with the following enhancements to improve safety and commercial feasibility.

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Those enhancements are: elimination of autologous human serum to improve consistency and predictability of cell yield; improvement in aseptic processing methodology to eliminate antibiotic requirements; methods to improve the consistency of chondrocyte isolation techniques; methodologies to enhance reproducible cell yield; and maintenance of appropriate differentiative characteristics.

[Slide.]

In this slide is depicted the Carticel process with supporting quality control tests and procedures. I know you can't read them, but the process steps are shown in the dark red, and the quality control testing points in yellow.

Initial processing of the chondrocytes begins with the receipt of the patient biopsy. Quality system personnel inspect the biopsy and assign a number unique to that patient. Batch records which will follow the patient's tissue throughout the process are generated. Primary cultures are initiated followed by carefully controlled cell expansions, and final processing of the chondrocytes includes graft assembly step, packaging steps, and labeling steps.

Final assembly of Carticel is completed in a clean room area dedicated to the Carticel final assembly

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procedures.

Throughout the manufacturing process a number of USP sterility tests are conducted at critical stages to monitor sterility. To ensure safety of each lot produced, a number of lot release criteria must be met before the release of the product.

Lot release tests include a vial inspection, assessment of morphology, determination of sterility and viability. The specifications for lot release are depicted on the next slide.

[Slide.]

Patient lots are released only upon compliance to these cell quality standards and after successful review and acceptance of all patient's cell processing records. Key indices of cell quality include percent viability of the expanded chondrocyte yield, density, morphology, sterility, and endotoxin. That last endotoxin should have a less than. I apologize.

Also, at prescribed periods, a well-characterized reference strain of human chondrocytes is processed to track, trend, and evaluate process consistency.

A number of quality assurance programs were implemented prior to regulation to ensure safety and consistency and reproducibility of the cell culture process.

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The following slides describe those programs conducted to validate the Carticel process.

[Slide.]

Those programs are aseptic processing validation to include media fills, validation of the cell culture procedures, qualification of patient and lot segregation procedures, the development of raw material specifications and qualification of raw materials, the definition of specifications used in the release of Carticel to surgeons.

[Slide.]

We have established programs for the training and certification of all cell processing personnel including quality systems personnel, validated test methods for quality control, calibrated and validated the cell processing equipment, validated those materials used in the shipping and preservation of the cells to the surgeon, developed and implemented a complaint/medical event monitoring system, and also inaugurated a broadly-based environmental monitoring program to protect the cells when they were in the clean room.

[Slide.]

So, in conclusion, we believe we have developed a strong quality and safety program that has been designed into the Carticel process, and that each step of the

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manufacturing process had been controlled to minimize variability, optimize reproducibility to enhance the robustness of the Carticel process.

Because of the incorporation of stringent quality standards over the past two years we have been able to process over 1,900 biopsies safely and consistently.

That concludes my talk, and I will now be followed by Dr. Tom Minas.

Patient Clinical Progress

DR. MINAS: Good morning. My name is Tom Minas. I am a consultant to Genzyme. My flight and hotel arrangements were paid to come here. Genzyme also sponsors data collection from my patients through our joint registry at the Brigham and Women's Hospital.

Today, what I would like to talk about is my clinical experience with alternative treatment methods and review of the literature results, very much like what Dr. Coutts went through, and talk a little bit about perichondrial grafting, which I have been involved with clinically.

[Slide.]

This is the lesion that we are treating today. We are treating full thickness, weight-bearing condyle lesions. These are lesions that go down to bone, involving injuries

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that are significant in size, and when we are talking about significant, here we have demonstrated one square centimeter. The lesions that are being treated in my practice are in the neighborhood of 5 to 7 square centimeters.

[Slide.]

The available treatment options for us are numerous: lavage and debridement, subchondral marrow stimulation techniques, which essentially are marrow-derived stem cells for the repair tissue, as well as autogenous tissues of perichondrium, periosteum, and then the technique that we are talking about today, periosteal patch with autologous chondrocyte implantation.

Of course, before we start, a natural history of a chondral injury is something that we all ask ourselves what is the natural history of a chondral injury and which patients should we treat.

Basically, the answer at this stage is unknown, and I will get into reasons why we don't really understand the natural history, although most orthopedists believe that left, a large chondral injury on its own will cause a degenerative joint. The size of these lesions which are predictive of a bad result really is not that well known.

[Slide.]

The factors that are important include size of the lesion, activity level of the patient, the alignment and stability of the knee, as well as a familial history of osteoarthritis which may predispose to earlier degeneration.

[Slide.]

Until the advent of the arthroscope in the 1970s, focal weight-bearing lesions really were not that well understood. Patients would have catching and pain and swelling, was often diagnosed as a meniscal or some other type of intra-articular pathology, but really when we developed the arthroscope, diagnostic classifications of full-thickness chondral injuries became available to us in the orthopedic literature.

[Slide.]

The size of the lesion really is important in my mind. Lesions that are greater than 2 square centimeters are significant in that these lesions cause weightbearing onto bone, and without shouldering -- which I will show on the next slide -- in a clinical series published for perichondrial grafting from Homminga, and the Britberg series from Sweden with Dr. Peterson, these lesions were significant lesions of 2 to 3 square centimeters in size, yet, over a three-year time course up to the time of treatment, they did not yet cause articular damage to the

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tibial articular surface.

[Slide.]

This is what I am talking about diagrammatically. Small lesions like this, which are probably 1 square centimeter or so, are often well shouldered by well-contained cartilage and no matter what you do to these lesions, they probably will have a very slow progression if they progress at all, and whether we treat these with lavage, debridement, or subchondral marrow stimulation technique, often they will result in improvement of symptoms.

The larger lesions, where the condyle is not becoming uncontained, and there is subchondral bone stimulation against the opposing articular surface, causes several effects - nerve stimulation of the bone and pain, vascular congestion and engorgement of the condyle with an aching sensation, and wear to the opposing articular surface.

[Slide.]

Here is one of my own case presentations noting such a large, full-thickness condyle injury greater than 2 square centimeters, and acutely, within a few months, you already see that there is already reciprocal tibial damage occurring, and this is certainly what I am thinking of when

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I talk about the condyle at risk of becoming a degenerative joint.

[Slide.]

The stability of the knee is also crucial to the degeneration of that joint. In personal communication with Dr. Lanny Johnson, his database is unpublished, but he has been collecting it for many years through arthroscopic video assessments and a computer base. In a nine-year follow-up of 2,266 arthroscopies, there were 516 ACL-disrupted knees accounting for approximately 23 percent of this series.

Acutely, he noted that there was a very small incidence of chondral injuries that were fresh fractures, about 1.9 percent, but in the long term, when these were followed up and arthroscopically assessed, there was almost 20 percent of these injuries demonstrated progression and larger, full-thickness condyle injuries, so that the unstable knee with the focal chondral injury is one at risk.

[Slide.]

This study that just came out last year talked about injuries that were greater than one square centimeter. In my mind, one square centimeter in my patient population is a relatively small injury, yet, here, 25, Grade III injuries, three, Grade IV injuries, so this is fibrillation down to bone and bone exposed, and lesions greater than one

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square centimeters, but they are not categorized further to say how large they actually became.

This was in an adolescent population at the time of injury, average 18 years old, followed up to the age of 32 on average. Twelve out of 28 of these patients demonstrated joint space narrowing indicating progression of disease, yet still clinically, they were still functioning well, so this intrinsic population of adolescent knees, who still have some intrinsic repair available to them, still demonstrated evidence of joint space narrowing radiographically despite reasonable function.

[Slide.]

Lavage has been gone over by Dr. Coutts.

[Slide.]

This is what we are trying to accomplish to release a lot of the mechanical agents that are within the joint, as well as the inflammatory mediators. In looking at published series in the literature, this has been helpful for relief of symptoms temporarily, but does not affect repair.

Dr. Jackson noted after his diagnostic arthroscopies in the seventies that up to 45 percent of patients would obtain pain relief for three to five years, and this was a subjective improvement in pain relief. This

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was not using any type of knee evaluation scoring system, and Livesley from the U.K. noted that up to 70 percent of people would have immediate relief of their night pain and aching at nighttime, but again this was short lived and by the end of one year, the pain would often return.

[Slide.]

A randomized control trial assessing arthroscopic washout and debridement versus closed needle office lavage was performed in the Chicago area by Roland Chang and his group, and they found that after evaluating patients clinically with HHS scores, in both groups, that their scores went from the high 40s to the mid-50s, and that overall there was no statistical difference between the groups in 12 clinical functional and global outcomes at three months and at one year, and that the cost difference between the office washout and the scope in the OR was about \$4,000.

[Slide.]

Debridement, as arthroscopy advanced and debriding instruments, mechanical, were developed to help to smooth and contour edges, such that catching symptoms and degeneration would not progress, these improved the results somewhat higher, but again this is a mixed bag of patients which had focal chondral injuries, as well as osteoarthritic

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knees, so that we don't have literature that specifically assesses debridement for focal chondral injuries.

Dr. Jackson noticed there was an improvement still, again, a subjective relief in improvement. The first paper to talk about an objective improvement was that by Baumgartner, and when they used HHS scores, they noticed that there was no change pre- and post-op in the patient outcome.

[Slide.]

A recent paper that just came out last year, published in Britain, was very illustrative in determining the outcome versus lavage versus debridement. This was a randomized study looking at isolated Grade III and Grade IV medial femoral condyle injuries, looking at the patient population that we are addressing today.

In this treatment option group, using a Lysholm score, there was a lavage effect that was very minimal in improvement and that was lasting for five years, which was much less than the debridement effect, and the debridement effect was measurable and lasted for up to five years.

[Slide.]

How about abrasion?

[Slide.]

Abrasion, again a motorized burr to basically

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stimulate subchondral bone bleeding, avascularization, and pluripotential stem cells, was originally written up by Lanny Johnson.

[Slide.]

His indications again are not for exactly the patient population that we are talking about. He indicates that this is good for a low-demand patient with night pain, unicompartmental bone exposed, and they must stay on crutches for two months postoperatively, non-weightbearing.

[Slide.]

His patient population that he reported on was in a patient population of over 60 years old on average, and in his questionnaire that he sent out, he found that only 12 percent of patients had no complaints after their surgery, that 66 percent still required pain medications, had loss of motion of the knee joint, continued to limp.

They required modification in their activity level, and they did have further surgeries after abrasion arthroplasty.

[Slide.]

Here is an example of an abrasion arthroplasty tissue in my own series. Even though there is repair tissue that develops and fills the defect, if this repair tissue is taken down, as was required here for recurrent symptoms, we

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can notice a fibrocartilaginous repair is noted on this safranin O staining where there is alternate layers of glycosaminoglycans, as well as just fibrous tissue.

So there is a repair which definitely occurs with abrasion tissue, but it is not often significant enough to allow return of high-level function in patients.

[Slide.]

Drilling. Again, drilling is reported mostly in the osteotomy literature as an adjunct to osteotomy. Here you can see a second look of the drilled areas of bone in which a repair tissue does fill, but this improves the osteotomy effect on its own slightly, so that 80 percent of patients at five years is a good result for an osteotomy. Drilling adds about another 5 percent as far as good and excellent results.

[Slide.]

Perichondrial grafting is something which I have personal clinical experience in. This was first published in the human clinical literature in 1990 by George Homminga from the Netherlands.

[Slide.]

His technique involves using costal cartilage and putting this, so that the germinative cambium layer is facing upwards into the joint up against the subchondral

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bone plate, glued down with fibrin glue and allowed to mature over time.

At one three, three biopsies which were performed demonstrated cartilage that looked very much like healthy articular cartilage, and there was a dramatic improvement in the Knee Society score. Age and subchondral bone penetration didn't seem to have an effect, but a recent finding was that radiologically, at two years, there was evidence of endochondral ossification in 20 out of 25 cases using rib perichondrium.

His two-year follow-ups were excellent and in personally discussing his results, he has been having the same problems that I have had in my clinical series.

[Slide.]

Here we see a four and a half year follow-up, and you can see an intra-articular area of bone formation at the junction of the graft, and at the time of open excision of the lesion, you can see here that there is endochondral bone formation right through to the surface. Here is the grafted area that was grafted nearly five years earlier with clinical failure being evident.

[Slide.]

We recently submitted for publication, the Mechanisms of Failure, and it appears that through Type X

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collagen expression there is bone formation in these grafts and that there are failures.

In a two- to five-year follow-up of this technique in 10 patients, we have had 6 clinical failure and 4 that are still surviving with regards to good function, 1 that is now demonstrating endochondral bone formation on X-ray and is developing recurrent symptoms; 4 have failed by endochondral ossification through to the surface of the graft, 1 has delaminated demonstrating the concern that Dr. Coutts had for integration of the subchondral bone, and 1 went central wear and degeneration of the graft.

[Slide.]

Periosteal grafting. The literature for clinical patients has been very scanty. A series that Dr. Shawn O'Driscoll just presented last month at the American Academy of Orthopedic Surgeons symposium on cartilage repair, he noted that he has done it now in 40 patients treated over a 10-year time period; 23 knee patients who were sent a survey, 15 responded.

These were lesions on average of 2 to 3 square centimeters for periosteal grafting alone without cells with the cambium layer facing up inwards toward the joint. In this survey of 15 patients, 9 felt they were satisfactory, 6 were clearly unsatisfactory and failures, and the failures

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in his series included 2 osteocartilaginous loose bodies resulting from the periosteal graft with poor integration, 1 deep infection with bone formation in the graft, and 1 with advanced osteoarthritis did not do well, 1 was a loose graft which did not integrate, and these were the failures in that series of 15 patients surveyed.

[Slide.]

So, in summary, I would say that lavage and debridement may help symptoms temporarily, but longer follow-up demonstrates that there is progression to degenerative joint disease, which is one of our concerns in that we want to restore tissue and preserve function and prevent this process.

This does not promote repair and rarely does an active patient return to a high level of sport with a lesion that is large.

[Slide.]

Similarly, marrow-derived therapies like drilling, abrasion, or microfracture, most of the literature on these topics is for advanced osteoarthritis, and only now are we getting reports for full-thickness chondral injuries.

The reports have been presented at meetings, and Dr. Rodrigo, who is using the microfracture technique has reported that 50 percent of patients with small injuries

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less than 2 square centimeters are able to return to sports with minimal pain; 75 percent are able to do comfortably with activities of daily living.

This essentially means that there is a 25 to 50 percent failure rate still using this technique in a small lesion, so that failures are often secondary to mechanical degeneration of the fibrocartilage repair between two and three years at follow-up.

Thank you very much.

Original Data from the BLA

DR. MOSCICKI: I will add my good morning to those that you have had already. My name is Dr. Richard Moscicki. I am the Senior Vice President at Genzyme, responsible for clinical, regulatory, and medical affairs at Genzyme.

Dr. Minas and Dr. Coutts have provided you just now with an excellent summary of the literature, and Dr. Minas, as well, his own experience, which suggests that current conventional therapies for cartilage repair in humans have not been satisfactory and unfortunately, do not readily allow direct comparisons.

I would like to begin by telling you about two surveys of orthopedic experience which we at Genzyme commissioned, that were conducted by two separate organizations independent of Genzyme, which I believe

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confirm the unmet medical need in the field of cartilage repair.

Until the slide is ready, I will tell you that the first of these involved the opinions of 16 experienced orthopedic surgeons who met preset criteria for that experience, which included publication in the field of cartilage repair within the past year in a peer-reviewed journal, and treatment of a specified number of patients, 15 patients per year for each of the past years.

Anyway, I will continue. In the opinion of these surgeons, it was quite clear that only 20 percent of the patients treated with current conventional techniques for cartilage repair were provided, in their opinion, adequate relief over the long term.

Rather, if one looked at the results that they expected at four years, 56 percent of the patients would result in pain and perhaps may not require such further surgical therapy, but 24 percent would by that period of time already require additional surgical treatment.

By 10 years, this worsened significantly whereby about 56 percent of the patients would require additional surgical therapy including treatment, such as osteotomy and even total knee replacement.

DR. HANLEY: Why don't we take a break here for a

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minute. I think we have a slide problem. You may have some disorganized slides back there.

I would also like to remind the panel that we do have a handout here that goes through the slides in order, and I think he begins on page 26 on the fax number, so that you may follow along.

If you would like to take a minute and go back and get your slides organized, I think it might be easier.

DR. MOSCICKI: Thank you very much.

[Recess.]

DR. HANLEY: If the panel members could come back to the head table, we would appreciate it.

I would like Dr. Moscicki to begin anew. I have asked him to start from the beginning, so that we may get all the information we need to appropriately assess what they are presenting to u.

So if you would start from the beginning with your slides, we would appreciate it. Thank you.

DR. MOSCICKI: Thank you very much, Mr. Chairman.

I am very pleased that I don't have to do the entire discussion from memory or use shadow puppets to illustrate visually.

[Slide.]

The first slide, once again, as I had mentioned

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before, I would like to start by telling you about two surveys of orthopedic experience which were commissioned by Genzyme to better understand this, and which utilized two independent organizations that were separate and separate from Genzyme.

[Slide.]

We believe that the results of these confirm the unmet medical need in the field of tissue repair. The first of these involved the opinions of 16 experienced orthopedic surgeons, and as I mentioned before, these physician had to satisfy preset requirements in having published on the outcomes of one or more treatments for the repair of articular cartilage in at least one peer-reviewed journal within the past five years, and/or had performed at least 15 procedures for the repair of articular cartilage in each of the past years.

[Slide.]

The results of this, to make a long story short, revealed that by four years it was the expectation of these surgeons that 56 percent of these patients would now still have pain although may not require surgical therapy, but 24 percent would require an additional surgical procedure by that point in time.

Their expectations were even worse at a 10-year

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outcome in which now 56 percent of the patients would have been expected to require additional surgical procedures including osteotomy and total knee replacement.

[Slide.]

The second of these was conducted for the recent OAS meeting. It involved the opinions of 86 Carticel-treating surgeons. These surgeons were also experienced in cartilage repair. As you can see, their expectations for the outcome with drilling and microfracture based on that experience suggested that by five years, only 66 percent of the patients, in fact, that 66 percent of these patients would have an outcome rated as fair or poor in their opinions.

Furthermore, for abrasion, at one year, only 46 percent would have been considered to have an excellent or good outcome, and by five years, 75 percent would then be considered a fair or poor outcome.

[Slide.]

This is quite consistent I think with what you recently heard from both Dr. Coutts and Dr. Minas, and I think we can then summarize the results of these surveys as demonstrating that currently used standard procedures provide inadequate results in the long term.

[Slide.]

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Now I would like to begin a brief review of the data presented in the BLA which we believe supports the proposed indication for the use of Carticel, which is the repair of clinically significant symptomatic focal defects of the femoral condyle.

I will start by briefly reviewing the major clinical points from the long-term data assembled in Sweden. Dr. Peterson has already given an overview of his own experience, the most recent analysis and evaluation of which was conducted after the inspection by FDA in Sweden.

Before regulation of the field, we conducted our own review of the Swedish experience for internal purposes and diligence. Given the flexibility expressed in the MAS guidelines, which you have just heard about, and discussion with FDA regarding such flexibility, we were encouraged to submit this data as part of the BLA.

Dr. McPherson and Dr. Micheli will subsequently review for you the other important components of that BLA.

[Slide.]

Now, the methods that we used in our own review was to look at all patients who were treated as of May of 1995 in Sweden. We used two different approaches. One was a retrospective data collection by an independent third party which focused on safety, and the second was a

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prospective data collection separate from the records to directly assess the patient's current clinical status using a questionnaire.

[Slide.]

This resulted in data regard 153 consecutive patients implanted in Sweden and represented a follow-up period from 10 to as long as 88 months. The majority of these patients were male, as is common, and were young adults with a mean age at implantation of 31. Of note, 44 percent of these patients had had prior surgical treatment of articular cartilage problems, and 25 of these patients required more than one prior procedure.

[Slide.]

Many of these patients had also had multiple defects treated, as you can see in this slide, but the important point is that these were large, clinically significant lesions with a mean defect size of 4.6 square centimeters.

This data included treatment of a number of different anatomical sites within the knee, but the majority of the defects treated were on the femoral condyle. Some patents with osteochondritis dissecans were also included.

[Slide.]

As far as safety, the review included any unwanted

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event which was noted in the charts of these patients from time of biopsy to the last evaluation in May of 1995. That represented a span of up to seven years.

Fifty patients were noted to report adverse event. None of these were probably or definitely related.

Thirty-one were considered to be possibly, predominantly because they occurred in the same knee as the implant.

Importantly, there were no serious infections, there were no joint infections, although occasional superficial wound infections were noted, and the great, great majority of these adverse events noted were consistent in occurrence and frequency with those expected after an open knee procedure.

In addition, Dr. Peterson has informed us that symptomatic hypertrophy occurs in approximately 5 percent of his patients, which requires arthroscopic shaving. In addition to that, he has noted that minor hypertrophy can be noted on incidentally, with second-look arthroscopies that he had performed.

[Slide.]

Now, the major outcome variable that was used in the patient questionnaire was the Lysholm score. This is a common scoring system for function of the knee which I am sure that many members of the panel are already familiar

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with.

However, for those of you who are not, I would point out that a maximum possible score on the Lysholm is 100. Most of the people in this room other than some of the patients perhaps who had not yet had this procedure would score in the 90s.

We would estimate that the baseline score for these patients would have been in the 40s, and I believe that has been confirmed to a large degree by Dr. Peterson's presentation earlier.

So at the time that this was conducted, at a mean follow-up period of 30 months after implantation, these patients had now achieved the mean score of 73, and if you look at the patients who have predominant treatment of the femoral condylar lesions either with or without ACL repairs, they were consistent with that overall mean score.

[Slide.]

We also looked at the data divided into the time that the patients had had at follow-up from the time of their implantation, and if one gets past the very initial group that Dr. Peterson had begun in this pilot studies, which included some of his initial failures during his learning process, and patellar patients, which are those described in The New England Journal of Medicine, that is

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described here as the group out more than 36 months, in fact, the average time for these patients at the time of follow-up was five years, then, you see that we get a very good Lysholm score out past 18 months.

Now, even if we look at this original group of patients, their Lysholm scores match the overall mean scores at that mean 30-month follow-up period. Furthermore, I think that when we looked at these patients on closer inspection, we could not find any evidence of degeneration of their clinical status over that period of time, rather the opposite, that these patients appeared to have improvement over the period of time.

[Slide.]

In response to the questionnaire, 75 percent of the patients reports that their knee, in comparison to before surgery, had had improvement, particularly those treated for femoral condylar injuries.

[Slide.]

In addition, these same patients treated for femoral condylar injuries reported that the effect of surgical procedure that had been performed had improved their knee status, and that constituted 79 to 80 percent of the patients.

[Slide.]

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So, in summary, I think that this data -- and we believe strongly so -- demonstrates that it is safe for autologous chondrocyte implantation, and that the data from Sweden support a favorable long-term outcome for autologous chondrocyte implantation repair of femoral condylar defects, and if you take into context the results that we have gotten from a survey of physicians' experience, as well as the comments by Dr. Minas and Dr. Coutts regarding the literature, we believe that these results are at least as good as, and probably superior, to that expected for current standard cartilage repair.

Thank you.

I will now introduce Dr. McPherson from Genzyme who will review with you both the basic science that supports this, as well as the histologic data.

**Histologic Evaluation of Alternative
Treatment and ACI**

DR. MCPHERSON: My name is Dr. John McPherson and I am Vice President of Research and Development for Genzyme Corporation specifically focusing on cell and protein-based therapeutics. I am also Vice President of Research for the Tissue Repair Division of Genzyme.

The objective of my presentation this morning is to review with the panel our interpretation of the

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preclinical and clinical histology data as they relate to the comparative quality of cartilage repair following conventional therapies and autologous chondrocyte implantation.

It is implantation to acknowledge in these introductory comments that while our assessment of the quality of tissue observed following chondrocyte implantation, the histological quality is similar to those reported by Dr. Poole in his briefing package to the panel, our interpretation of these data are different.

Dr. Poole has interpreted the histological picture to provide evidence for widespread degeneration in patients with the biopsies analyzed by histology. Our interpretation is that these data are consistent with either imperfect regeneration or a repair procedure that is in progress, tissue repair in progress.

[Slide.]

Now, it has already been pointed out that tissue repair of any kind requires cells, and in the case of cartilage repair, the availability of cells is very limited, and therefore, conventional therapies, such as drilling, microfracture, or abrasion involve recruiting cells from the subchondral plate. In the case of drilling, bone marrow cells move into the defect site; in the case of

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microfracture and abrasion, cells from the subchondral tissue move into the defect site.

New approaches, including things like perichondral grafting or autologous chondrocyte implantation, as in the case of Carticel, use cells that are either articular chondrocytes themselves or cells that have a chondrogenic potential.

[Slide.]

Now, the clinical outcomes with conventional therapies have already been reviewed, but the bottom line is that at early time points, conventional therapies provide excellent to good results at the one-year time point in about 60 percent of the patients, about 20 percent of these patients, provide excellent to good results at later time points, for example, at four years.

So, the message here is that in conventional therapies, while the clinical outcomes can look promising at early time points, the reparative process does not provide for long-term clinical benefit.

[Slide.]

Now, the type of tissue that is generated following conventional therapies is called fibrocartilage. Fibrocartilage is very cellular in its makeup, it has a fibrous appearance, and is generally not particularly dense

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in terms of the extracellular matrix organization.

[Slide.]

This is in contrast to hyaline cartilage, which normally make up the articular surface. Hyaline cartilage provides a very dense matrix, it is not as cellular, and the cells within the matrix are organized in a vertical array, which is shown here.

Now, the histological picture provided by fibrocartilage or hyaline cartilage is a consequence of the extracellular matrix components that comprise these respective tissues.

[Slide.]

Hyaline cartilage, as has already been pointed out, is composed of a particular group of collagens, predominantly Type II collagen along with Type VI collagen and Type IX collagen. In addition, there is a chondroitin sulfate proteoglycan called aggrecan along with hyaluronic acid and link proteins which form large macromolecular aggregates that influence the compressibility of the tissue and provide for its elasticity.

In contrast, fibrocartilage which is generated by conventional therapies is comprised primarily of Type I collagen, it does contain proteoglycans, but they are different from the cartilage-specific proteoglycan aggrecan.

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They also contain hyaluronic acid and link proteins to lower degrees than normal cartilage.

The consequence of these differences in extracellular matrix components between hyaline cartilage and fibrocartilage is that it is generally considered that fibrocartilage has inferior biomechanical properties and therefore does not provide for long-term clinical benefit.

[Slide.]

Now, in the MAS cell guidelines, as Dr. Siegel has already pointed out, one of the key points to be considered by the panel is that evidence of normal or repaired structure may be accepted as evidence of efficacy where there is a high probability that it will be associated with clinical benefit.

Now, the data that I am going to present you, we believe provides evidence of a repaired structure that correlates with clinical benefit. The FDA, in their briefing document to the panel, has implied, however, that totally normal regeneration should be considered as evidence for true restoration of function.

Now, I think it is important for us to point out that we feel that that is an unreasonable expectation. If you look at tissues such as liver and bone, which have the highest level of regenerative capacity in terms of

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functionality, they do not provide a histological picture that is identical with a high degree of reproducibility to that observed normally.

So, the real question we believe should be do we have evidence that we are generating a repaired structure that is different from fibrocartilage and that correlates with clinical outcomes in the patients that have been treated.

[Slide.]

Now, again, this is one slide that summarizes a great deal of data. These data represent results from about 20 patients that have been evaluated both histologically and from a clinical outcomes point of view. These are patients that include both femoral condyle lesions and patella lesions.

These data are derived from the early patients treated in Sweden with greater than two years follow-up, and the results show that about 70 percent of the patients have excellent to good results at greater than two years, whereas, about 6 percent have reported fair to poor results.

[Slide.]

In the majority of patients, the type of tissue that has been observed has been called hyaline-like cartilage. This tissue has a ground glass appearance upon

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safranin O staining, that is similar to that observed in the normal hyaline cartilage, however, the cellular organization is different from hyaline cartilage, normal hyaline cartilage.

You will see evidence, for example, of cell proliferation or cell cloning, as Dr. Poole pointed out. Our interpretation of these data is that this represents a tissue repair in progress. Dr. Poole's interpretation, as we understand it from his report, is that this is evidence of tissue degeneration or osteoarthritis because, as a matter of fact, cell proliferation and cloning is observed in osteoarthritic situations. But again, this, we believe, is a hallmark of repair as opposed to a hallmark of degeneration.

[Slide.]

In some specimens that have been looked at histologically, there is a fibrous tissue on the surface of the implant, and subjacent to this fibrous tissue you see this hyaline-like cartilage. This fibrous tissue, we believe is remnants of periosteum that have been incorporated into the healing tissue.

[Slide.]

At higher magnification, although it is difficult to appreciate it because the lights are somewhat bright, you

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can actually see at higher magnification fibrous tissue and subjacent to the fibrous tissue you see evidence of hyaline cartilage. Again, we think that in many of these specimens, this represents incorporation of the periosteum into the healing defect.

Dr. Poole has interpreted at least in some of these situations that this is again evidence of degeneration.

[Slide.]

Clearly, in some patients we do see evidence of fibrocartilage or fibrous tissue, as shown in this slide, a very cellular kind of tissue and a very fibrous or fibrotic kind of an appearance characteristic of fibrocartilage.

[Slide.]

If we do a correlation of the clinical outcome compared to the tissue type, we see that there is a good correlation between excellent to good clinical outcomes at an average time of about three years, four months, for patients who have hyaline-like cartilage. In contrast, patients that have fibrocartilage have fair to poor results.

So, we believe that there is a reasonable correlation, in fact, a strong, positive correlation between the histological picture you see with hyaline-like cartilage in the majority of patients and a good to excellent outcome

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at approximately three years, four months.

[Slide.]

The question has been asked why should articular chondrocytes provide a superior clinical result compared to alternative therapist. We believe there are at least three reasons for that.

First of all, articular chondrocytes are normally responsible for the production and maintenance of hyaline cartilage.

Secondly, following expansion in culture, chondrocytes retain the ability to produce extracellular matrix components that are characteristic of hyaline cartilage. This is a key component to the strategy of Carticel, in other words, expanding the number of cells available to be implanted into a site and having those cells retain the capacity to produce extracellular matrix components that are characteristic of hyaline cartilage.

Finally, alternative therapies use either endogenous or transplanted cells that are not differentiated, for example, bone marrow derived cells, or are poised for endochondral ossification in the case of perichondrium in some other transplantation techniques.

Now, I think we will all agree that articular chondrocytes are normally involved in the production and

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maintenance of hyaline cartilage, but what is the evidence that following expansion in culture, chondrocytes retain the ability to produce hyaline cartilage matrix, and what is the evidence that alternative therapies will potentially generate ossification or result in ossification?

[Slide.]

Over 15 years ago, Benya and Shaffer reported in a paper in Cell, that dedifferentiated chondrocytes re-express their differentiated collagen phenotype when cultured in agarose gels. Basically, these investigators were the first investigators to observe that isolated articular chondrocytes would dedifferentiate, stop making Type I collagen when you put them on plastic and stimulated them to proliferate, but when you remove them from tissue culture plastic and put them in a suspension culture, these rabbit chondrocytes had the capacity to redifferentiate and produce components that were characteristic of hyaline cartilage, such as Type II collagen.

[Slide.]

Over the last 15 years, a number of investigators have confirmed and extended these observations with cells derived from a number of different animals, and recently we have observed that chondrocytes that are expanded using the Carticel production procedure also have the capacity to

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redifferentiate in vitro.

This particular experiment is an RNase protection experiment in which we monitored messenger RNase for Type X collagen, Type II collagen, Type I collagen, and Type IX collagen.

In monolayer culture, human articular chondrocytes dedifferentiate in a similar fashion to that, that has been reported for rabbit articular chondrocytes and chondrocytes derived from a number of other animal species, however, after a few weeks, these cells redifferentiate and express Type II collagen, as shown in the third lane. Alginate is a suspension culture system similar to that used by Benya and Shaffer 15 years ago that allows one to evaluate cell redifferentiation in suspension culture.

[Slide.]

Not only do the cells turn on the proper genes in the case of Type II collagen, for example, this particular aminohistogram shows Type II collagen staining using an antibody specific for human Type II collagen.

There is a second antibody that is conjugated to Texas Red and what you see is that the nuclei of these cells are stained blue with the Hoechst dye. At two weeks following suspension culture there is very little Type II collagen matrix production, however, at four weeks and six

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weeks, you can appreciate that the amount of red in this picture increases consistent with an enhanced production of Type II collagen, again characteristic of hyaline cartilage.

Now, these experiments are in vitro experiments which provide circumstantial evidence that articular chondrocytes, that are expanded according to the Carticel processing procedure, can indeed redifferentiate, but what is the evidence that indeed they do so in vivo?

[Slide.]

What we have done is to evaluate autologous chondrocyte implantation in the dog model of cartilage repair. In this model, we have introduced 4-millimeter defects on the trochlea of adult mongrel dogs. Here is a defect here, there is one here in the trochlear groove, more difficult to appreciate.

We have evaluated the healing of these defects over time using either cell implantation or no treatment.

[Slide.]

At six months, what you see in this particular dog that had no treatment is some level of spontaneous filling of the defect here and here.

[Slide.]

There was a trend at six months for improved filling of the defect. This is an animal that was treated

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with its own chondrocytes in a strategy similar to that used for the human implantation procedure. The original defect was here and here. As you can see in this particular animal, the fill was substantially greater.

At six months, this trend was observe. As a consequence of spontaneous healing in the animals and also as a consequence of degenerative disease that developed in these animals, it was difficult to appreciate differences between treated and controls.

In some of these animals we actually implanted cells that were retrovirally labeled in a way that we could detect these cells subsequent to implantation. There has been a question what is the evidence that the cells you put into the defects survive and actually produce matrix components characteristic of hyaline cartilage.

We evaluated these retrovirally labeled cells at six weeks, 13 weeks, and then at six months. I should tell you that using this retroviral reporter gene called beta galactosidase, we were able to treat the histological sections with a substrate that is converted to a blue color by the enzyme, the beta galactosidase enzyme.

What we see here at six weeks, and we also saw at three months, is evidence of the cells implanted in the defect, since we do see blue stained cells, in the margins

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and base of the wound. In addition, we see evidence of Type II collagen production in the vicinity of the cells.

These particular slides were counterstained with an antibody to Type II collagen. This antibody was conjugated to a histochemical marker that provided a brown color, so you can see this brown area here is consistent with Type II collagen production in the vicinity of the blue cells, the implanted cells. You can also see obviously that the margins of the wound stain brown because of the Type II collagen that is present in the preexisting hyaline cartilage.

So we think that this does provide evidence that indeed the cells do survive and can produce hyaline matrix components, extracellular matrix components consistent with hyaline cartilage.

[Slide.]

The question has also been asked why not utilize chondrogenic cells derived from perichondrium and periosteum. The answer to that question is actually several-fold. First of all, we believe that the pathway of repair is unpredictable using cells using other than articular chondrocytes.

Dr. Minas has already shared with you data showing that in perichondrial graft, there is a high propensity for

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endochondral ossification, chondrocyte hypertrophy.

[Slide.]

This is a slide from one of Dr. Minas' patients. This is hyaline cartilage that was in the margins of the original defect. The periosteal graft was placed here, and after about two and a half to three years, you can see a wave of endochondral ossification that is moving forward into the defect site which ultimately leads to failure of these kinds of grafts.

[Slide.]

We isolated this area of the specimen and stained it with an antibody to Type X collagen, which is a hallmark of endochondral ossification, and based on immunohistochemical staining against Type X collagen, we see that in the wave of ossification evidence of Type X collagen production and a pericellular organization in this portion of the issue.

We have also done RT-PCR kinds of experiments to quantify Type X collagen mRNA in both articular chondrocytes and in growth plate chondrocytes, as well as periosteal cells.

[Slide.]

This particular strategy is a very sensitive PCR-based strategy that allows us to detect mRNA in cell

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samples. What we see in suspension culture is that whereas articular chondrocytes do not make Type X collagen, growth plate chondrocytes make a large amount, and also cells derived from the periosteum also have the capacity to produce Type X collagen.

So, I think it is important for everyone to recognize that the default pathway in terms of tissue regeneration may be towards endochondral bone formation as opposed to articular cartilage repair. We have additional data to support that hypothesis. Unfortunately, I do not have time to review that at this time.

[Slide.]

In conclusion, I think it is important to realize there has never been a double-blind, randomized placebo controlled, multicenter trial performed on any of the therapies currently used to treat either partial-thickness or full-thickness cartilage injury of the knee.

Therefore, we are forced to rely on published results and survey data to understand what to expect with these standards of care or conventional therapies, and the data from these published results and surveys indicate that standard surgical procedures, for example, drilling or microfracture, and abrasion, provide short term palliative relief with fibrocartilage, but progressively degenerate to

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osteoarthritis in the majority of the patients.

We believe that the degeneration is a consequence of the lack of biomechanical durability of the tissue that is produced in these wound sites by conventional therapy.

[Slide.]

In contrast, articular chondrocyte implantation provides a unique preprogrammed reparative pathway that involves production of hyaline-like cartilage in the defect sites.

We believe that the efficacy observed with autologous chondrocyte implantation is a consequence of this hyaline-like matrix production which is more similar to normal human cartilage and has better biomechanical properties.

Thank you.

It is my please to introduce Dr. Micheli, who is going to review our registry.

Twelve Month Registry Report

DR. MICHELI: Chairman Hanley, members of the panel, and guests: I am very pleased to summarize some of the data in the patient registry to date.

[Slide.]

As of November 30th, we have some good information I think. Again, this is a summary of a lot of information

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which is available in a newly-prepared packet as of January. The charge of this registry is to measure clinical outcomes for patients treated with autologous chondrocytes in general orthopedic use, evaluate the factors that contributed to successful outcomes, and then, in turn, to communicate these clinical findings to participating surgeons in particular, as well as the orthopedic community.

[Slide.]

The registry board consists of five of us. We are geographically scattered across the country. I come from the Boston Children's Hospital. We have had two meetings to date on this information you are going to hear about in the next few minutes.

[Slide.]

Our responsibility is, as requested by this company, was to look at clinical review and advice regarding data collection, look at subgroupings that will become clinically pertinent in the future, as an example, and provide medical review of the registry data including particularly analysis for both safety and efficacy, and then, of course, to appropriately and accurately interpret this data to the orthopedic community.

[Slide.]

We have six- and 12-month patient assessment data,

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and our primary emphasis in the next few minutes will be on the 12-month data. We will use some of the six-month for comparison.

The technique used for analysis was questionnaire. This company has been very aggressive in getting the questionnaires back from the surgeons they have trained, and then use this process, as well as from the general public, and I think they have done a good job of collecting this information, and those of you who are involved in such studies know it can be a very difficult situation.

[Slide.]

The rating scale used is a Modified Cincinnati scale, modified because the Cincinnati scale was primarily a sports medicine scale, and the rating that was asked of the participants was basically from zero to 10, 10 being of course high and good, and zero low, and similarly, from the patient survey component, 2, 4, 6, 8, 10, once again 10 being the highest, and both the surgeon and the patient at each step of the way are queried as to what they feel their outcome is.

[Slide.]

To date, 133 surgeons have performed this procedure in the United States, and 13 in Europe, performed this procedure which has been reviewed, there have been

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several more since.

There has been 100 percent compliance with 12-month data collection, which is a good number. Of the patient compliance 121, or at the six-month follow-up mark as of November 30th, 42 at the 12-month follow-up, 84 percent compliance with six months and 86 percent with 12-month data collection from the patients.

[Slide.]

Prior surgical procedures, of the 241 patients who have received implants until November 1996, some of whom of course are not included in this data as far as follow-up, these patients had 305 procedures performed, 215 of them had debridement or lavage, 90 had abrasion arthroplasties with drillings or microfracture, and the mean patient score prior to their intervention was 3.21, the mean Cincinnati clinician score of the assessed surgeons was 3.30.

[Slide.]

Most of these patients had one defect being treated with this implant system, some had, as you see, two and even greater than two defects. The majority or about 80 percent are single defect being treated.

Defect location, by and large, the clinicians have followed the advice of the Genzyme Company in their initial training, and are working on medial and/or lateral femoral

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condyles. There have indeed been some patellar or trochlear treatments and also tibial surface treatments. As you heard from the Swedish data, this may be your less favorable group which needs much more concentrated rehabilitation work if you are going to work on the patella, and so forth.

[Slide.]

Defect area. These are, by and large, large lesions. As you have heard, favorable results can sometimes be obtained with no treatment with a smaller lesion, 4 to 6 cm in size, 15.6; 2 to 4 cm, 35; more than one-third of these lesions, and 23 percent were less than 2 cm in this instance, but, of course, judged by the clinician treating that patient to be clinically significant and therefore worthy of treatment.

[Slide.]

A busy slide, and we will take a little bit of time going through this. Overall condition at the 12-month, again compared to some extent to the 6-month. You see the baseline clinician evaluation, 3.00, and these numbers of the 12-monthers, and at 6 months, the score was at 6.06 and the same group at 12 months, 6.91, a statistically significant difference between 6 months and biopsy score, and again between 12 months and 6 months, statistically significant on the part of the clinician evaluation.

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Again, the scores on the patient surveys have gotten better. There is a statistically significant difference between 6 months and biopsy preoperative site timing, but between 12 and 6 months in the patient assessment, there is not a statistically significant difference, although there certainly is a trend there as you can see.

[Slide.]

Overall condition, looking at the patient, combining the clinical and the objective/subjective, at 6 months, improvement 84 numbers and 72 percent, and 12 months, of these 35 patients, 4 and 2, 85 percent of the 12 months feel that they have been improved or felt to be improved, no change 9.8 percent, worse 4.9 percent.

[Slide.]

Patient assessment of symptoms, looking at pain and swelling is a different criteria in their questionnaires, a significant improvement between 6 months and biopsy, and again between 6 and 12 months, rather similar as far as their symptoms of pain.

As far as swelling, significant improvement at 6 months, and the same degree of improvement between 6 and 12 months, and of course, in this instance, no fall-off, no return of swelling at 9, 10, 11, 12 months, and so forth, as

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you sometimes see with other techniques.

Knee examination by the clinician, 12-month results. These are 12-month data. Presence of joint line pain, 85 percent of these patients had joint line pain before the procedure, and at 12 months, 30 percent still had joint line pain, which is a significant difference. Presence of effusion, 77 percent of them had swelling of their knees prior to their procedure, presumably on a regular basis, and now 6 percent report swelling of the knee at 12 months.

So that is certainly encouraging trends in this pattern of data over this period of time.

[Slide.]

As far as the relative safety of this intervention, again, by a great number of different surgeons on a great number of different patients often with rather unfavorable lesions, 11 patients had adverse events possibly related to autologous chondrocyte implantation.

The overall adverse event rate in this group of patients was 3.5 percent, and no joint infections were reported. I would remind you clinicians in the room, of course, that 3.5 percent from an arthrotomy procedure is very much in the range of general arthrotomies of the knee as far as rate of complications.

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[Slide.]

Going down through the adverse events, looking at them in some detail, adhesions and fibroarthrosis. You have heard a little bit about some of these complications, number 10, related to ACI, no. This is the opinion now of the clinician queried. No, 6 of them, and 4, yes, thought by the clinician to be related to the implantation process.

Of course, hypertrophic changes, a similar pattern. Delaminations, 1, 0, 1, yes. DVT common to many arthrotomy type procedures, and so forth, wound infections not thought to be related to the intra-articular intervention.

Joint infections zero, two superficial wound infections. Post-op fever, one. This one patient had an FUO and was labeled as possibly related to this, but never was diagnosed as having a specific organism, and ultimately cleared up with recurrent effusions.

[Slide.]

The reoperation rate, 30 patients were reoperated in this initial group, 9.5 percent of the total have undergone at least one reoperation of the treated joint, and 2 patients have had their implant removed. One of these was a patellectomy because of a patellar implant, and of course, the implant was removed also. The other was a patient who

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had persistent mechanical symptoms.

[Slide.]

The reoperation rate, to dissect this out a bit, the reoperation was often for manipulation or lysis of adhesions in a good majority of these, and there was some hypertrophy in this group of over 300 operations which required intervention. Again, breakdown as to whether the surgeon felt they related specifically to the implant and no/yes, 8 no, 9 yes, 5.4 percent.

Patch reattachment was done in one case --

[Interruption of electric power.]

DR. MICHELI: I think that is fine as far as the summary.

[Slide.]

In summary, 375 implants were performed by 122 surgeons during this initial period. Needless to say, many of these surgeons are on a learning curve with this particular technology which is technically demanding.

Average baseline status of patients was poor initially and then 66 percent had at least one attempt at implant prior to this, so this was also a patient group with a lot of difficulties, more challenging patient interventions, and 85 percent of these patients had been reported to be improved at 12-month follow-up. It is

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12-month data, but it is very well worked 12-month data.

Eighty percent improvement in pain scores at 12 months, and 11 had had adverse events, at least possibly related to ACI. The statisticians who have worked this are an independent company in Cambridge. They are also available here for further questioning and discussion of the epidemiology for the further discussion of this process.

We feel there is an excellent patient and physician compliance thus far with this process of follow-up evaluation, physician and patient outcomes that correlate to the early Swedish clinical experience as you have heard earlier, and the cumulative data support the use of autologous chondrocytes in treating femoral condylar defects in particular, and whether other interventions may have indications in the future with certain other technologies, and so forth, remains to be seen.

This is basically a reproducible result with a multicenter experience.

Our final presentation of this session, Dr. Moscicki is going to talk the proposed multicenter study which Genzyme has been looking at in recent months.

Thank you very much.

DR. HANLEY: Thank you. Dr. Micheli, before you step down, could you tell us any affiliation that you might

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have with the sponsor?

DR. MICHELI: Yes. I am on the registry board and therefore my way was paid here, and the patients I was supposed to see today, I will be seeing tomorrow night and Saturday. Thank you.

DR. HANLEY: Thank you.

Proposed Comparative Clinical Study

DR. MOSCICKI: Thank you, Dr. Micheli.

[Slide.]

I would like to start my discussion at this point in time by making some particular notations. You have now heard a brief summary of the data in the BLA, and earlier, you heard the overview of the results from Sweden by Dr. Peterson.

We strongly believe that this evidence that has been presented to you, and is in the BLA, satisfies the guidelines that have been put forward by the FDA for approval of MAS cells. Let me just take a moment to review some specific points on that issue.

The long-term data that has been presented regarding Sweden provides very good evidence of a long-term benefit for these patients. Furthermore, the data from the U.S. registry, that Dr. Micheli just presented, involves multiple surgeons and confirms the level of short-term

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benefit that was already observed in Sweden following along very similar lines. In fact, both results appear to be at least as good as, or probably better than, the current alternatives that have been discussed several times today.

If we look at the evidence for normal or repaired structure, Dr. McPherson has outlined for you that the histologic data clearly indicates the presence of repaired structure, and his basic science data I think strongly supports that this repair structure is the likely result of chondrocyte implantation.

[Slide.]

As far as systemic toxicity, we do not have the data, but that has not been required as Dr. Siegel has in fact pointed out earlier, but rather I do believe that the data shown provides that there is a very clinically acceptable safety profile involved with this technique.

When you examine that combined with the data regarding the benefits, as well as the correlation between the benefits and the presence of repair structure that have been presented today, I think it is very clear that there is a favorable risk to benefit ratio.

The indication, as specified, in fact has already been confirmed by the FDA to be a serious illness. On the issue of historical controls, I think that we and others

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would probably agree that there are no useful historical controls that would allow a very direct comparison.

However, the preponderance of data that I think has been discussed and presented today would suggest that the qualitative clinical outcome data related to that of these alternative treatments indicate only short-term palliative benefit and long-term clinical failure, which I think is very distinctive from the story that you have just heard.

In fact, if we take apart the components that occur during the procedure of autologous chondrocyte implantation, for example, the initial debridement and lavage, I think it is very clear that that does not account for the long-term benefits or the repair structure.

Furthermore, the data that is available on periosteum and its role does not suggest that this would likely be the major point that would provide the benefits that have been observed in the long term.

[Slide.]

Now, in the remaining few minutes, I would like to tell you about a comparative clinical study that Genzyme made a commitment to well over a year ago in its conduction. During that period of time, there have been countless hours spent in discussion with orthopedic investigators, and in

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fact, we have already had three intense and extended meetings with a group of orthopedic investigators to come up with the current design, which I will tell you about very quickly.

It is a multicenter effort. It will involve 300 patients, 150 patients in each of two arms. This is based on an alpha of 0.05 and a beta of 0.9, and prediction of a substantial dropout rate due to long-term follow-ups involved.

There will be these two arms, one consisting of Carticel, and the other consisting of alternative conventional treatments today, and the investigators have chosen microfracture or abrasion arthroplasty to represent that.

There is a cohort design using an assignment of the patients to each of the cohorts, which I will mention in a little bit more detail later. This is a long-term study involving a follow-up of up to 60 months and will involve the use of a common and well-accepted clinical rating scale, the Modified Cincinnati scale, with evaluations both by the patient and the clinician, and in addition, will involve the use of objective measures, such as a standardized MRI protocol, the use of standard instruments, such as the SF-36 to measure quality of life, and importantly, follow-up

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arthroscopy with biopsy both of the area of repair, as well as the surrounding normal tissue being recommended.

[Slide.]

This is a list of the current investigators. I think you will recognize many of the names that are present on this list. They are well respected within the orthopedic community and well recognized for their experience in clinical research.

[Slide.]

Now, what about the design of this, what led us to formulate this two-arm study involving the current use of a control group involving these alternative therapies? Our investigators have pointed out that these, in their opinion, represent the current standard of care, they have a similar mechanism of repair, comparable outcomes, and therefore are combinable likely as one group, although that will be tested during the study.

Why not choose, despite its scientific attraction, a control arm which involves the use of periosteum alone? Well, after many discussions on this subject with our investigators, it was very clear that there is no data really regarding the use of periosteum alone in the treatment of patients with these types of articular cartilage defects.

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Even the technique of Dr. O'Driscoll, who has been mentioned before, actually penetrates the subchondral bone plate. Furthermore, there was concern by the investigators regarding the mechanism of failure of current knowledge regarding some periosteal and perichondrial grafts, and that is endochondral ossification.

But finally, and perhaps most importantly, given the fact that there is no evidence that the use of periosteum alone would benefit patients, to subject those patients to the risk of an open arthrotomy and a subsequent six-month period of rehabilitation was felt to be medically and ethically unacceptable to the participating surgeons.

[Slide.]

As far as the treatment assignment method, I would like to describe that quickly, if I can. Essentially, each site involved in the study would be assigned a specific number of patients, and there would be two teams of surgeons, one responsible for performing the Carticel procedure and trained in that, and the other trained and familiar with the alternative technique.

For example, at the Hospital for Special Surgery, Dr. Warren and Dr. Haas have been assigned to do the Carticel procedure, and can enroll only up to 10 patients. An alternative team has been assigned microfracture.

If a patient presents to Dr. Warren or Dr. Haas and accepts entry into the study after informed consent, then, these patients would be assigned to Carticel. However, patients that then, after reviewing their options, request specific treatments, these patients must be excluded.

[Slide.]

The rationale for this system is that it reduces as much as possible selection bias in this arena, and yet includes an important random element. We have carefully discussed the use of classical randomization because again of its scientific attraction. However, all agree at this point that it is not feasible and would likely significantly decrease the ability to accrue patients into the study.

Furthermore, by a system that uses surgeons that perform their preferred technique, the highest skill level is assured for each procedure, an important issue in surgical clinical research. Dedicated surgeons and their use eliminates to a large degree the bias in surgeon preference for one procedure versus another.

Finally, there is a logistical issue related to reimbursement issues and delay possibly after random assignments.

[Slide.]

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Now, the inclusion/exclusion criteria are listed in your briefing package for Genzyme, and so I won't go through them in detail because of time elements, however, I will say that these have been carefully designed to provide an area of a homogenous group of patients, as well as to remove as many as possible confounding variables.

We will be studying a group of patients who have intact subchondral bone plate, and I will just simply point that out.

[Slide.]

This gives you a schedule of the evaluations that are planned in the study. You will notice that in particular, the principal analyses will involve the Modified Cincinnati knee scale, and in particular, as a primary efficacy variable, a cartilage related subcomponent of that, as well as histology, and so the first of the principal analyses will be performed at 36 months with subsequent statistical principal analyses with the clinical variables at 48 and 60 months.

[Slide.]

Finally, we have decided and agreed upon after discussions with FDA to hammer together a single rehabilitation protocol for all of the three procedures involved in the study.

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Thank you very much. We are looking forward to getting further input from the advisory panel regarding this protocol, which already represents a substantial and large amount of input from the orthopedic community.

Thank you.

I might add that that does conclude our presentation, Mr. Chairman. Thank you very much for the opportunity to have presented all of this information to the panel.

DR. HANLEY: Thank you.

We are scheduled for FDA presentations before the lunch break, which was scheduled for 12:30. I think in view of the time and the extensive amount of time we have in the afternoon for discussion, I would recommend that we break now for lunch and instead of coming back at 1:30, come back at 1:15, and we can proceed with the FDA presentation and follow that with our discussion.

[Whereupon, at 12:15 p.m., the proceedings were recessed, to be resumed at 1:15 p.m.]

A F T E R N O O N S E S S I O N

[1:20 p.m.]

DR. HANLEY: Thank you. I appreciate everyone coming back a little early. I think we have adequate time this afternoon to have the presentation by the FDA and the third discussion of the issues at hand.

At this time, I would like to turn it over to the FDA representatives to make their presentations concerning Carticel.

Dr. Eda Bloom.

Presentations by FDA

Product

DR. BLOOM: Thank you, Dr. Hanley, committee members, and guests.

[Slide.]

The review of Carticel has presented an entire spectrum of novel and challenging issues for our review, and I would like to take this opportunity to say that the License Committee, whose names you see listed here, has met these issues with both flexibility and diligence.

[Slide.]

With this slide, I would like to introduce to you a brief overview again of the manufacturing process. I will skip that which you have heard from Dr. DuMoulin.

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At this point, I would like to mention that this is just as an introduction into the clinical material which you will hear presented from the FDA standpoint shortly and which you have already heard presented by Genzyme, and that is the material which is our major concern this afternoon.

The product and manufacturing issues have been examined both through review of the BLA file and through an inspection of the establishment which was held in December together with members of the New England District Office of the FDA.

[Slide.]

In brief, the production of the autologous chondrocytes used for implantation encompasses these steps here from biopsy through implantation, the major point being that cells are expanded ex vivo.

[Slide.]

The importance of lot release criteria are to ensure the potency, purity, and identity of the product, and with this in mind, Genzyme has developed a number of lot release criteria to address these issues, and Dr. DuMoulin presented to you a slide in which there were a bunch of yellow diamonds indicating at which point sterility was being tested.

[Slide.]

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The characterization of the final product in the case of this novel therapy of cartilage cells has been an interesting challenge for the company and for the FDA alike, now at this current time being addressed by morphological assessments, however, Genzyme has agreed to continue to develop more objective identity assays which will offer further characterization of the product.

[Slide.]

You have also heard clinical material, clinical information that has been gathered both in Sweden and in the United States. The production of the product used in these two instances have some differences, that is, the media additives used in the culture, the length of culture, and whether or not the cells have been cryopreserved.

However, comparisons have been provided to us which show the differentiation under nonadherent culture conditions which you have already heard is important for the production of the particular type of collagen required by hyaline cartilage and the cell yields seem to be significantly the same between the procedures used in Sweden and those used in the United States.

With that, I would like to introduce Dr. Richard Lizambri, who will present you with the FDA analysis of the clinical data.

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Thank you.

Clinical

DR. LIZAMBRI: As our electronic equipment is warming up, we can start to see the first slides.

[Slide.]

Basically, today, I will be giving the BLA clinical presentation and in my introduction I will have a few background pieces of information to say, and then we will very briefly review a few points from the sponsor's efficacy assessment on the Swedish data that we heard earlier this morning.

Then, we will go into much more detail regarding the medical reviewer efficacy assessment and the safety assessment based on Swedish data. Then, there will be a very short discussion of the historical controls, and this will be by Dr. Schwieterman, and we will also have some very brief comments on the registry data and the proposed clinical study.

[Slide.]

So, as I said, the first portion will be a review of the sponsor's data, and I wanted to emphasize that in the sponsor's data there are really two data sets. The original submission was based on the Swedish patients, and that is related to the fact, as you have heard, the product was

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developed in Sweden.

In this data set, there were 153 patients and the data were looked at retrospectively, and it was really an open-label study.

All the patients who had been treated with the product from 1987 to May 1995 were included in this review, so it was a rather comprehensive review of the experience. the other part of the information is the U.S. registry data which was submitted as an amendment to the BLA.

There is some data on the six-month follow-up which we received some initial portion of in December, and the 12-month follow-up, which we received in January, and then more actually last week, so we won't have a complete discussion of all the 12-month data.

[Slide.]

For the Swedish patients, we wanted to go over what were the available data sources that we had to look at these 153 patients. As you heard, and I want to explain in somewhat more detail, a questionnaire was sent to patients who had achieved at least 12 months after treatment.

[Slide.]

The questionnaire, we will talk about a bit more in the next slide, but 82 patients have data available. For the biopsy data, we will be looking at the 22 patients who

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has a series of biopsies, and we will be discussing. There were some additional biopsies, but we felt it was more necessary to concentrate on these patients because they were consecutive series.

Finally, there was a retrospective case report form that had 153 patients.

[Slide.]

Of these Swedish patients, as many of you in the audience know, the first 23 were published in The New England Journal, their experience was published. Of these 153 patients, 11 had a second procedure done.

I wanted to just spend a moment and mention that the sponsor did review it with the second procedure, as well as the first. We elected to eliminate the second procedure from consideration mainly related to the fact that we felt if there were any individual characteristics of a patient that would predict that patient's outcome, the outcome might not really be independent from their first assessment, so therefore, to get a more pure data set, we just looked at the first outcomes, and we will have some further discussion on that.

Finally, it is important to remember that many of the patients has concurrent procedures, and these procedures are important because they could potentially confound the

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analysis, and one of the ways that the sponsor and we only attempted to modify the assessment would be to create different subgroups by procedure type, and we will also discuss that in a little more detail.

[Slide.]

Here is a slide, however, with some of the procedure groups as defined by the sponsor. I won't spend a lot of time on that, but I do want to mention that there were a total of 153, and the sponsor defined the femoral condyle patients as 74.

You can see that there was another group specifically cut out for the people who had anterior cruciate ligament repair and some other groups as well.

[Slide.]

The questionnaire that was sent to these patients represents the following types of questions. The patients were assessed by knee function by a question. They were assessed by the effect of surgery by a question. The Lysholm scale, you have already heard about, and some of the other scales.

[Slide.]

The data were collected as follows. Patients with greater than one year follow-up were sent a questionnaire. A total of 124 questionnaires were sent. The first

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questionnaire was sent to a group of 62 patients who had achieved greater than one-year follow-up at the time of mailing, and 59 responded.

Sometime later a second group of questionnaires that were slightly different were sent to an additional 62 patients, which were different patients, and 39 responses were obtained. This probably relates to not receiving all the responses by the closing date of wanting to submit the application.

Of these responses, there were 98 total responses, the sponsor entered 82 into their database and analyzed these. We did request information on these other 16 patients. At this time, it has not been available to us for review.

[Slide.]

Looking very briefly at one of the questions, the knee compared to before surgery by the patient's response. Just to talk about the content of this slide for a second, notice this is first surgeries only.

The sponsor analyzed, as I said, first and second surgeries. Because we received the data in an electronic form we were able to abstract out only the first surgeries, and I am showing this slide mainly so that you can remember some of these numbers when we come to the medical reviewer

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independent assessments, and compare them.

You can see here there were a total of 72 patients for the first surgeries who answered this question. You can see, looking more importantly at the femoral condyle group alone, we can see that the answer of the question was improved in the 70th percent range, in these admittedly smaller numbers, 23 out of 31, that is probably the number to remember, but roughly in the 70 percent range, and the total for all the groups was also in the 70 percent range.

[Slide.]

There was another question that was asked, what was the effect of this procedure, improved, uncertain, not useful. Once again, notice 74 patients total out of this 153 data set actually had data available for this question.

Looking at the femoral condyle group alone, again, 27 out of 34, and once again in the 70 percent range. I did want to mention, for both of these questions, when we looked at the first and second surgeries combined, which was what the sponsor originally submitted, there was not really that much difference. It was in the 70 percent range, just about the same.

[Slide.]

To discuss some of the biopsy data, as I said, core biopsies were obtained in 22 of the first 23 patients.

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We analyzed these biopsies independently in some detail because we felt this was representative somewhat of a consecutive series. Only one of the patients had a missing biopsy of the first 32.

There were additional 6 patients who had a core biopsy, but we did not elect to analyze them as carefully in outcome compared to clinical and functional outcomes, which we will discuss later, because we were not really sure what was the precise indication of biopsy, and that could have affected the clinical and the arthroscopic procedures that were performed on these patients.

There were non-core biopsies that were obtained incidently at follow-up arthroscopies for a variety of reasons. There were many other tissue samples, but many of them turned out not to be available at the later date of follow-up.

[Slide.]

Finally, just to discuss the case report form, it is important to remember that many data points were not available in this retrospective case report form. Numerous parameters, however, were surveyed and they were collected by an independent contractor.

At this point, I did want to emphasize, as you can imagine from these data, that although it did give us a

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certain amount of picture of what had been happening to these patients, there did seem to be certain additional pieces of information that we wanted to know to better understand the outcome when the product was used.

[Slide.]

For instance, we felt that we would like to know additional data on the functional status of the baseline. Because of the method which the sponsor used, using a questionnaire, we really understood the outcome really at a particular time point. We also, therefore, did not have information on the 71 patients who hadn't submitted a questionnaire for analysis.

In addition, we felt if we could understand the history of the entire clinical course of a patient, we would have a much clearer picture of the clinical response. In addition, we wanted to get the full arthroscopy reports, so we could have another separate type of independent assessment of the outcome to the procedure.

[Slide.]

In light of these desires for more information, we felt that we would be able to attain this by looking at the original patient records. Prior to doing that, we defined certain outcome measures, and we defined these prospectively before we looked at the data.

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One was a term which we considered functional, which is a very simple explanation. This represents the level of patient function and the patient's symptoms, as well. In addition, the arthroscopic measures, which we labeled objective as a shorthand method for talking about this group, were related to actually looking at the transplant and seeing what the effect was over time.

In addition, we defined certain analyses that we will be talking about in more detail, and the following slides will go into that.

[Slide.]

Of the 153 patients we reviewed all the records that were available. These included the original physician notes, the arthroscopy reports. These records were translated into English. As I mentioned, myself and one other reviewer spent two and a half weeks in Sweden making sure that we were able to see all the data. Basically, some of the data had to be translated on site because of Swedish regulations.

After we attained these pieces of data, then, we began to construct an electronic data set, and we also entered into the data set our assessments of the patient outcomes. Once these were available, then, we began to be able to perform a variety of analyses, and that will be what

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we will be talking about next.

[Slide.]

Prior to going into that, though, I did want to give a very brief discussion of the difference between the types of analysis, techniques, and what the possible outcomes would be.

For instance, in patient 1105, the sponsor assessed the patient as improved based on the patient's questionnaire, and the patient did, in fact, respond that they were improved. This was approximately at 12 months. On the review of the entire data, however, the patient had another major procedure at six months involving the fact that the transplant site had been loosened, and an abrasion arthroplasty was done underneath the site of one-half to two-thirds of the transplant.

So, at this point, we and the medical reviewer consider the patient a failure because of the second procedure. At 12 months, perhaps related to the procedure, the patient was somewhat improved as the questionnaire indicated, however, by 14 months the patient started having pain again, and eventually, the transplant at 20 to 24 months roughly was removed.

So, these are some of the possible differences that could come about between looking at an individual point

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and seeing the entire clinical course.

Looking at our assessment, then, of these records, just as the sponsor did, we divided into procedure groups, but ours are slightly different, and will discuss that, and then we will discuss the outcome measures.

[Slide.]

Just to emphasize our definition for femoral condyle, the patients in the FC category received a femoral condyle transplant only. Other procedures, such as even debridement, let's say, of a separate lesion on the patella without transplant would get you in a different category, so this was more a pure category of people who just had femoral condyle lesions.

[Slide.]

The patients having only patella would be in the patella category.

[Slide.]

I will go very briefly over this slide and go to the next one, but we had 50 patients -- that was a little quicker than I expected -- but we will get the same numbers this way. Down at the bottom these are my numbers. So 50 patients were in the FC category by the medical reviewer group, so these categories go straight down here.

All these numbers right here, 50 out of 153. The

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sponsor got 74, as you recall, and just looking at the differences, looking down this diagonal of larger numbers, this is the line of identity. If they called it femoral condyle, and we called it femoral condyle, it landed on this line. For instance, patella versus patella.

So, you can see in this quadrant, there were really not much differences, but in this quadrant, the differences tended to be that the femoral condyle defined by the sponsor got spread out into a number. These patients seemed, on a more careful assessment of their history, to have some history of osteochondritis dissecans.

These patients tended to have some other procedures involved. Many patients had debridement of their patella, but no transplant.

[Slide.]

I wanted to discuss, then, what were our outcome measures. One was the functional outcome, as I said, the patient's overall ability to function with level of activity and symptoms. The other one was an objective outcome based on arthroscopy, sometimes based on repeat surgery. Then, in addition, histology, and finally a safety assessment.

We also had the consideration of what was the appropriate length of follow-up to judge the outcome of the patient. We wanted to be sure to distinguish any transient

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from durable responses.

As you heard earlier, and you will hear more from Dr. Schwieterman later, there does seem to be some response to other types of therapies, so we wanted to make sure we were following up patients at a sufficient time point to understand that this response was more durable.

In addition, there was a fair degree of rehabilitation involved in this, and so we didn't want to have a time point that was too soon before the patient had really had an opportunity to recover function.

[Slide.]

So, of the three types of assessments that we did, this is the first type, so I want to walk you through this. We were trying to look at the functional outcome at two years. So, the possible outcomes that the patient would have based on our review of the individual data were resumed all activities. This is actually a fairly high level of function, would involve, for instance, oftentimes returning to running or other high levels of function if the patient did that at baseline, but it was based on the patient's baseline.

Patients that were not able to resume their complete function, but had some improvement were in this category. Patients that did not have improvement were in

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this category, and some of these patients were worse. The sponsor had broken that out separately, but that is not the way we chose to look at it.

We chose a window, then, of 22 to 28 months. If a patient had a follow-up visit during that time period, then, we have the patient an assessment in this window, and that was a total of 51 patients.

For instance, even if a patient had a much longer follow-up time, but didn't hit this window, then, we left them out of the assessment because we wanted to capture a relatively clear snapshot of this point in time since these patients had a very wide degree of follow-up times.

[Slide.]

So the outcome of this was that looking down this column, then, you can see a total of 51 patients, as I said, and in the group that resumed all activities, this was 14, but looking at our subgroup now of just femoral condyle, we can see 2 out of 13 were able to resume all activities. An additional 5 had some improvement, 5 had no improvement, 1 was unevaluable or unknown based on the amount of follow-up data available.

[Slide.]

The additional type of functional assessment that we did, we called No. 2, was based on the end of follow-up.

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This was taking a look at any patient that had 18 more months of follow-up. Remember, this would vary widely. Some would have 18 months naturally, some were out to '94. This is somewhat farther than the sponsor's maximum patient, but this is because we did an independent assessment of data at a later time point, and we actually saw patients as late as a follow-up visit of November 1996. There were 86 patients in this evaluation.

[Slide.]

The outcome of this, as you see again, 86 patients, and looking first at the femoral condyle patients, we see 7 out of 26 were able to resume all activities, an additional 8 had some improvement. If we want to compare this -- which we will do later to some of the sponsor's outcome -- we could probably think of this category as patients who have shown some improvement and collapse these categories and compare it with the sponsor's numbers of improvement which we will do later.

You can see that these were the numbers that we got for this group, which we felt was quite important, and there are other groups, as well. You can see the osteochondritis dissecans seemed to have patients that fit in this category.

[Slide.]

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The final type of assessment, the third type is what we call the objective assessment for want of a better term. We perhaps could have called it the arthroscopic assessment, but there were some surgical assessments, as well.

This allowed the direct assessment of the structure. The types of patients again were the end of follow-up, so they mirrored the types of patients from the efficacy assessment too.

The types of outcomes were one that we called microscopic integrity. This didn't mean, however, everything returned to perfection. Oftentimes the tissue was somewhat softer than the normal tissue. But it did mean that the defect was full and that it seemed that it was up to the normal surface and other significant problems did not seem to be present.

For major defects, these were more severe, that would likely be interfering with the action of the transplant to replace. This might be things like part of the transplant being loose or missing, et cetera.

Minor defects would be between these, not a major problem with the transplant, but other things that were going on. As I said, this is 18 or more months of follow-up on all these patients, 86 of them.

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So we can see in the next slide what were the outcomes.

[Slide.]

There are 86. For the category of microscopic integrity, which represents, as I said, not perfection, but filling of the defect and no other major problems or even the relatively minor problem, we can see 2 in this femoral condyle category out of 26 attained this status.

Out of the entire group, 4 out of 86. In addition, we can see the ones, 13 out of femoral condyle group, 13 out of 26, 50 percent, who had minor defects. When we looked at these numbers, we tried to think a bit of what analysis would help us to understand better what was going on here.

Remember, here is an unknown category. Many patients, especially later patients who were doing well, did not have a follow-up arthroscopy. So, potentially, some of these patients, had they had an arthroscopy, could have entered these categories. So this is something where these numbers might be slightly higher.

But in addition, one other phenomenon that we found that was helpful to explain what was going on, this is the phenomenon of hypertrophy, and for those people who are expert in cartilage physiology, this does not represent the

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chondrocyte hypertrophy, but it represents one of three things - either extra tissue on the graft or heaped-up edges at the edges of the graft or just an additional amount of tissue throughout the knee.

This once again is at 18 months of follow-up and once again by the medical review treatment groups, and we can see, looking again at these 86 patients, a total of 37 or in the 40 percent range had some hypertrophy present, and 6 out of 26 in the femoral condyle alone group.

This was a phenomena that helped to explain why not as many patients were in the microscopic integrity category. The exact etiology and the ultimate outcome for this hypertrophy, I think is still somewhat up in the air.

[Slide.]

In addition, we performed an assessment of the clinical functional outcome versus the objective or arthroscopic. So, here along the top we have the resumed all activity, some improvement, et cetera, et cetera, and here, down this side, these are the arthroscopic categories and microscopic integrity.

So we can see looking right down this column, the percentages relate to the column. So of the people with resuming all activity, 4 out of the 25 or so were able to have microscopic integrity, an additional 12 had some minor

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defects, et cetera.

So we can see that there did seem to be some association here that if you resumed all activities, you did tend to have more of a chance to be in this category rather than in the major defects category, whereas, the people with no improvement tended to be more in this area.

[Slide.]

We performed a number of other analyses, but I won't go through them all, but basically looking at this data set of 18 months or more, we did not find any association of difference in outcome by gender, no association of difference in outcome by age, by history of meniscal surgery, by failure of previous procedure, by area of the defect, or by the number of cells.

I am going to show three slides now. The first two are somewhat complicated, and I will go through them to help you out.

[Slide.]

This represents now an assessment of outcome based on cells per square centimeter given, so that in this analysis, which is somewhat complex -- and I will try to simplify it -- we did not really see an association between the clinical outcome and the number of cells per unit area given.

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However, we did notice that this patient over here was quite an outlier. This is a patient that received a large number of cells in a small lesion, and so we took the liberty of doing an analysis with removing that patient since that patient had a very influential outcome on the entire analysis.

In that case, we did see some association, which is what this line shows, to the clinical outcome, and the association was that less cells tended to have a somewhat better clinical outcome in this analysis. As I said, we did have to remove that point to get this. Without removing that point -- this is actually a somewhat different point than the last slide -- but without removing that, the analysis didn't really show an association.

[Slide.]

This is a somewhat complex slide, but I can simplify it. This is a Kaplan-Meier plot. We are losing the top of that, but these are the 95 percent confidence intervals, and what it is talking about is what was the need for a follow-up procedure of any type.

Most of these procedures were minor ones, such as a repeat arthroscopy, often to treat symptoms of the hypertrophy which were often related to crepitation or catching, and approximately 17 months was the median, so

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that after the procedure of transplantation, the patient was usually coming back at a certain point for arthroscopy.

We eliminated from this analysis any arthroscopy that was done simply for diagnostic purposes as part of the follow-up of patients. These were arthroscopies that were performed because the patient was having a complaint. Naturally, any surgery that the patient had, such as removing a transplant, would also be included in here.

[Slide.]

We did want to compare our assessment of the clinical functional outcome, the medical reviewer versus the sponsor by the questionnaires. This morning the sponsor also had some other types of clinical assessment based on I think the Britberg clinical assessments.

Here is the collapsed table that I did promise you. This is the reviewer category of improved where we collapsed resumed all activities and some improvement. You would be adding down this column, and the percentages would refer to this column.

So, 37 patients would be in the reviewer improved category, and the sponsor improved category based on the question how does your knee compare to before surgery in the questionnaire, would be improved in these two.

So, here is where the agreement was with reviewer

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improved and sponsor improved. You can see 37. An additional 7 agreed where the reviewer stated not improved, and we collapsed the categories of the sponsor's analysis for all the ones, no improvement, worse.

So, these are the patients that are different. There were 4 patients here. On closer analysis, many of these differences were related to differences in the technique. As I said, for patient 1105, that is one of these 4 patients that the reviewer felt was not improved, that the sponsor had counted as improved.

This table then does show some association between what the sponsor got with their technique of sending questionnaires and what the medical reviewer came up with an analysis on doing individual patient assessment, and doing these other analyses that we discussed.

[Slide.]

We are going to talk next about the histology data. I am going to have one more slide before we hand over to Dr. Poole, and he will give a descriptive analysis of the histology. Then, we will have a comparison of the sponsor versus our consultant assessment.

That slide actually might be out of our presentation now for purposes of time, but we will have a histological versus patient outcome assessment.

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I did want to set the stage for Dr. Poole, that we are really going to be concentrating on the core biopsy series of the 22 of the first 23 patients. There were these 6 additional biopsies, but since they were at various patients, decided to concentrate on this series, and there were some non-core biopsies which we won't discuss, but perhaps if there are discussions, we could discuss them later.

I will turn this over to Dr. Poole.

Histological

DR. POOLE: Thank you, Dr. Lizambri.

What I am going to do is first show you some examples of the specimens I looked at, and as I indicated in my report, I also looked at them with Dr. Lizambri present, so that I could discuss my findings and observations with him at the same time. I felt this was very important. But I was entirely responsible for coming up with the final assessment and making my determinations.

These slide are my slides from my collection, nothing to do with the sponsor's specimens.

[Slide.]

Basically, we are looking at a normal articular cartilage here stained with safranin O, but sometimes the staining varies. Here it is not extending so intensely to

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the top of the section.

This is a 20-year-old male. This is femoral condylar cartilage. This is healthy cartilage, intact articular surface, some increase in intensity of staining for proteoglycan around the chondrocytes. The characteristic organization of the chondrocytes that you can see here. Then, we have subchondral burr down at the bottom that I am not showing.

[Slide.]

This is a 69-year-old male from the same site. There is evidence of very early fibrillation here, very early indeed. It is very slight, and this is very characteristic of people of this age. These specimens were taken at autopsy.

You can see, by and large, there is clear evidence of a hyaline cartilage, evidence perhaps of a little less staining, but it is an intact tissue, maintaining normal hyaline organization, and I stress hyaline organization.

[Slide.]

This is a specimen. I am using the nomenclature of the sponsor, and it is Slide No. 18, and it is a patella specimen from a 27-year-old female.

I looked at a total of 25 specimens. As Dr. Lizambri said, there were 22 in the series, and I looked at

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25, and there were 4 that looked normal. This is the articular surface. This is part of another specimen.

As I indicate in my report, the actual preparation of the specimens in my opinion was very poor. The staining was extremely variable. The mounting left a lot to be desired. There were quite a lot of bubbles, and so on, in many of the specimens, but there were usually several specimens per slide, and I was able to look at them, and I have satisfied myself that I could see them clearly, but the staining was really quite inferior quality.

However, you can see an intact articular surface, a very nice hyaline cartilage. I saw that in 4 out of 25 specimens. I would grade that as a Grade zero. So there are 4 specimens, and I will show you my report as an overhead in a moment that all members of the panel and the sponsor should have.

[Slide.]

This is Slide No. 1. Now, this is a patella from a 27-year-old female. It is 12 months. The previous one was at 17 months. This is at 12 months. What we are looking at here is very much a fibrous tissue. This is not a hyaline cartilage. Based upon a lot of other work that people have done, we would expect there to be very little abnormal contents of Type II collagen, if it is present,

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probably a lot of Type I collagen, but we just don't know.

There is some staining here, but to be quite honest, I wouldn't rely upon the staining because it was so variable and different dyes were used, and not the dyes that I would recommend. I would strongly recommend the staining procedure, as I indicate in my report, of Dr. Rosenberg's, safranin O and fast green. That is the staining procedure that we used in our specimens that I identified this morning.

So this is a very fibrous tissue, and I graded it as Grade V, and I will discuss my grading in a moment.

[Slide.]

This is another patella specimen. I am showing these purely as examples of different types of tissue, for no other reason. This is a 27-year-old female at 12 months, fibrocartilage. It is also Slide 1. So within a given specimen, there could be differences, both fibrous tissue or fibrocartilage, or we could have hyaline cartilage and fibrocartilage, or hyaline cartilage and fibrous tissue. So I am showing these purely as examples of the tissue classification. This is a Grade V specimen, as I said.

So we are looking at the fibrocartilage, and you can see the lacunae quite well defined. You never see this in fibrous tissue. You can see a very collagenous matrix,

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something again that we normally never see in a hyaline cartilage even if it is degenerate and has lost its proteoglycan.

We don't see this classic appearance of the matrix that other speakers identified this morning. So this is a fibrocartilage as opposed to the previous slide, which is fibrous tissue.

[Slide.]

Here we have again one specimen, two slides. This is femoral condylar tissue and it is from a 26-year-old male, and this is after three years. What we are looking at here is the articular surface as best as one could recognize it. Often, in these specimens, it was difficult to identify clearly recognizable articular surface, which was a concern, because as I pointed out this morning, the presence of the articular surface and what is happening to it is very, very important, at least in my opinion.

We can see evidence of vertical fissuring, splitting, degenerative tissue.

[Slide.]

We are going to go deeper now, and the subchondral bone is down at the bottom here. We can see evidence of a more hyaline cartilage as opposed to a more fibrous or semi-fibrous cartilage up here. This is more hyaline down

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here.

I think there are about three specimens I was able to look at where they included a small part of the subchondral bone, and in every case there was very good integration with subchondral bone which was good to see. This is after three years, and we will look at the next specimen.

[Slide.]

This is Slide No. 5. The last one was Slide T1171. This is Slide No. 5. This was in a situation where the femoral condylar cartilage was sampled in a 40-year-old male at 22 months, and that is what you look at here. This evidence suggests that this may well be a persistent articular surface.

There is some cloning of chondrocytes here. The staining would suggest that it is very deficient in proteoglycan, but again in fairness, because the overall staining process was so inferior, I wouldn't attach any significance to the staining with respect to proteoglycan content. That is something that really has to be addressed in future studies.

But there is evidence of a hyaline tissue, of cloning and degeneration as one can see here.

[Slide.]

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Let's look at that six years later, and this is an example. This is six years later, the same specimen. A Grade V, I graded it, and you can see clearly a very degenerative process, splitting. I saw this frequently. Wherever I saw hyaline cartilage of the articular surface, I saw this early, clear fibrillation, very much like what we would see in osteoarthritis, and I saw evidence of cloning frequently associated with the splitting. The previous slide also showed evidence of cloning.

[Slide.]

This is a specimen six years later, so if the sponsor proposes that what we are looking at is part of a repair process, and we see more degeneration on the follow-up as do, or we see equal degeneration on the follow-up, it is hard to imagine that this is a repair process if the degeneration is maintained or increases.

In several specimens we had the opportunity to look at follow-up cases, and the degeneration was as pronounced, by and large, if not more pronounced. So this is six years after that previous specimen, and we do, in fact, see evidence of more clearly defined hyaline cartilage. Again, I have concerns about the technique, and I think clearly this issue has to be addressed very carefully.

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[Slide.]

This is T1471. This is an 18-year-old male, femoral condylar sample. This is after four years, and this is subchondral bone down here, and it is Grade VI. It is very degenerate as you can see.

[Slide.]

In this case, adjacent cartilage or neighboring cartilage was also sampled, and this was done in a couple of cases.

[Slide.]

This is what the neighboring cartilage looked like. This is subchondral bone, more of a fibrocartilage, clearly extremely degenerate. There were two cases where there was neighboring cartilage outside the defect.

The concern, therefore, that is raised here is, is this degenerate process a consequence of the initial defect, is it a consequence of the management of the defect, or is it a consequence of a combination of the two, because the normal cartilage surrounding the defect, as you can see, and I saw it in two specimens out of two which we were provided with, it was far from normal. It is extremely degenerate, characteristic of what we would see in a very degenerative process.

The other point I would like to make before I

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switch to the overheads is in no case were there any specimens where I was able to assess the integration of the new cartilage with that already present. So it is impossible to address the fundamental issue of whether or not there was biological integration of this new cartilaginous tissue with existing cartilage.

There were no biopsies presented to me to enable me to address that issue, but wherever there were biopsies going into subchondral bone, there were three, there was integration with subchondral bone, but we know nothing about whether there is integration with the cartilage, and that is really critical, a critical issue.

I am now going to switch to the overhead.

[Overhead.]

This is the grading system that I use, and I stress that we have far from a perfect grading system, but this is an arbitrary grading system because we had to come up with at least some semiquantitative assessment of what we are looking at.

This is in all the reports. What I did do was to revise it on February the 15th, because I hadn't included a consideration of fibrillation from the surface to the mid-zone, and fibrillation, the splitting from the surface to the deep zone, and I added this in. It didn't affect the

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initial scores, it changed a couple of the follow-ups.

I address the articular surface cellularity, splitting in the mid- and deep zones, presence of hyaline or fibrous cartilage or fibrocartilage for thickness. If it was 50-50, 50 percent fibers, 50 percent hyaline, I scored that appropriately, and I give indications here of maximum possible scores of 6 if it hyaline, very degenerate, or 8 if it is fibrous, large acellular, very degenerate, compared to more healthy cartilage where there is very limited fibrillation, if any, and where the maximum score would be 1.

[Overhead.]

Using that scoring system, and I deliberately didn't use the Manken [phonetic] system, because that has been devised for studies of osteoarthritis, and I don't want to see any bias here, so I came up with my own separate system. Again, I stress it is an arbitrary system, but it gives us something to work with.

Basically, these are the classifications. As I said, I looked at 25 specimens. In addition to the 22 in the series, I looked at 3 more, and these are the ones with the normal scores. There were 4 that looked like normal hyaline articular cartilage.

The majority, as you can see, were in the region

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between 3 and 6. There was one at 8 that fell into the maximum degeneration category.

So, looking at these specimens, I observed cartilage that looked in the majority of cases far from normal.

[Overhead.]

I will just mention a couple of points. I alluded to it a moment ago. Where specimens were examined from normal cartilage of the same condyle, degeneration was pronounced similar to, if not greater than, that seen in the implanted site. So I have concerns about why this neighboring cartilage is so degenerate, and this is something that we need to address. As I said, I have concerns although I feel that they didn't affect my assessment as I performed it, but my assessment could have been far improved had the histological techniques been of a higher standard.

So, basically, I think that concludes my summary statement with respect to my review of the specimens. I did it in what I consider to be a constructive and critical fashion based upon my experience as a cartilage watcher.

Thank you.

[Slide.]

DR. LIZAMBRI: This is a slide from the sponsor's

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briefing packet. It might have been actually slight different this morning, and the sponsor will have to let us know. I think there is an additional patient here, perhaps this patient was 6 here, but they used now the clinical ratings from Britberg, and these are not the ratings from the questionnaire.

These were from Dr. Garlick, their consultant, did the patient have hyaline-like cartilage at all or fibrocartilage, so they had seen that in their analysis, 14 patients had some hyaline-like cartilage, and 12 of those had entered the excellent to good category from Dr. Britberg's assessment. As I said, it was not really based on the questionnaires that they had used.

[Slide.]

Using, however, Dr. Poole's histology, we used his descriptions and we abstracted from him did the patient have hyaline cartilage, mixed hyaline and fibro, or just fibrocartilage, and then the clinical outcomes.

Basically, one important way is to kind of look first right across here. These percentages refer to up and down, but actually the other interesting percentages would be this way, which we will kind of work out as we go.

If the patient had hyaline cartilage, two of these patients had entered this category. Three had entered this

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category and three had entered this category. This is a total of eight patients, so this is probably a little over 30 percent roughly.

[Slide.]

Coming down this way, if they had just fibrocartilage, you can see that this is fairly similar in the outcomes, in other words, that the patient who had just fibrocartilage resumed all activities -- and I have to enter this one proviso from our statistician, remember these are extremely small numbers, so perhaps we shouldn't look at the percentages at all -- but if we just look at the numbers and get an idea, and remember one last thing, that it is very uncommon to get biopsy slides of any kind in any way, so this is a unique resource to look at regardless.

So we have 2, 2, and 3 with the fibrocartilage, 2, 3, and 2 with the hyaline cartilage, and about the same with the mixed. I think one other thing, if we wanted to compare it to the sponsor's, let me go back just briefly because this is such an important point.

Remember, this was the sponsor. They had a hyaline-like versus fibrocartilage, so if you look at these numbers, instead of having a different slide, if you just kind of combine these numbers, so if we add these two, so it's 4, 5, and 5 compared to 2, 2, and 3, so any hyaline

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cartilage when we add these 2, plus comparing it to completely fibrocartilage, we really see from this analysis that there doesn't really seem to be an association between the clinical outcome as measured by resumed all activity, some improvement, or no improvement by the medical reviewer and the histological outcome.

However, in the next slide we show something that the sponsor didn't really talk about.

[Slide.]

Looking at the medical reviewer arthroscopy outcome and comparing this to the histology, once again -- remember the category of microscopic integrity versus minor defects and major defects, once again let's look at these numbers right across the row, and forget these percentages because they represent the column, but we could just make our percentage as we go if our statistician would allow us, looking at the patients with hyaline cartilage alone, we can see 2 had microscopic integrity, 5 had minor defects, and none had major defects.

With the mixed picture -- well, let's look at the fibrocartilage first because that is the biggest contrast. None had achieved the category of microscopic integrity, and the patients were in these two categories.

Of the mixed picture, the mixed were actually

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somewhat shifted toward this way as well. So we did see that -- we can't really say it is an association because the numbers are so low -- but we did see that the patients with the histology as abstracted from Dr. Poole's report, did seem to indicate that you were more in these categories when you had the histological outcome of hyaline cartilage, and you were more in these categories with the fibrocartilage, but remember once again the numbers are quite small.

[Slide.]

Going now to adverse events, this is an independent assessment not related to anything that the sponsor has done, but as I reviewed the 153 patients, I noted any adverse reaction that I thought was something that should be noted, and of that, 34 of the 153, and in the 20 percent category, did have at least one side effect.

Before I go to the next slide which distinguishes some of them, I want to mention, however, that we did not use the hypertrophy in this category because we discussed that separately.

[Slide.]

We can see that the side effects, such as adhesions, superficial wound infections, were of the nature that one might expect from an open procedure of this type, so it was not really something that was beyond things that

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you might expect with the type of procedure that the patient had.

Jumping ahead very briefly for a second, the U.S. registry data seemed to bear out these types of adverse reactions.

[Slide.]

Just to summarize, then, what we have seen in the Swedish patient data. The sponsor had reported on their questionnaire something slightly over 70 percent of the patients had improved by questionnaire. The sponsor associated the patient improvement with the presence of hyaline cartilage in the slide which we just saw and which the sponsor presented earlier.

The medical reviewer did a completely independent assessment based on the original Swedish data, and we confirmed that there was a high incidence of functional improvement consistent with what the sponsor said by different analysis technique, but we did not see an association between the functional improvement and the presence of hyaline cartilage.

In addition, we did want to note that many patients has this phenomenon of hypertrophy, and finally, that the adverse event profile seemed to be within the range that one might expect for a procedure of this type.

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[Slide.]

Finally, one point that can't really be missed is that in the submission, there was a large degree of missing data, the follow-up of the patients was quite variable, the number of biopsies available were relatively few for analysis technique, the slides themselves were somewhat poorly prepared, as Dr. Poole has said, and we had no real control group to help us fully interpret the data.

So the next step of the presentation will be Dr. Schwieterman, who will go into some of the clinical literature and will then discuss some aspects of the registry and the proposed clinical trial.

Historical Control

DR. SCHWIETERMAN: Good afternoon.

[Slide.]

I am going to go very briefly over this body of data, mostly because we have heard this before, but secondly, we are very anxious to hear the committee's opinion about the matters that we are about to discuss here including the utility of registry data, the proposed trial design, and so forth. So forgive me if I go fast, I am going to try to get the essence of it, so we can get to the meat of the discussion this afternoon.

[Slide.]

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The purpose of the literature review here is to really help the committee discuss both the safety and efficacy of Carticel and the proposed clinical trial design. I view it actually as a compliment to the committee's expert opinion given that the sponsor submitted a single-arm, open-label study, and as Rick just mentioned, there was no historical control group defined.

They did submit a wide body of literature, however, which I will try to briefly summarize here. This brief literature review obviously is not exhaustive, and we hope to at least complement your opinion by presenting it and stimulate discussion in this regard.

Finally, I just want to emphasize what Dr. Siegel mentioned. It is appropriate to consider historical controls for some MAS cell therapies, as outlined in the MAS cell policy document.

[Slide.]

There are a number of difficulties with the literature review. As has been mentioned, there is few control studies, no consensus on optimal study design, different patient populations, clinical outcomes, outcome measures, follow-up durations make review of this literature extremely difficult, and I think the sponsor has done a diligent job in looking through it.

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We have looked through it ourselves and trying to glean what we can from this data, but it is just very difficult. Direct comparisons are problematic, so we will go study by study.

[Slide.]

This is just the overview of what I am going to talk about. I am going to start off with the conclusions and then supply the literature beyond that just to show you where I am going.

The outcomes for periosteum and perichondral grafts, the outcomes for subchondral drilling and abrasion, the outcomes for debridement and lavage, I will speak to quickly. Then, I am going to give a brief summary of this, discuss in a couple of slides the U.S. registry data, and then comment very briefly on the proposed clinical trials, so we can get to the discussion.

[Slide.]

The general conclusions are these. There are many treatment modalities that exist. Many of these provide short-term benefits as many people have alluded to. Some may provide for longer term benefits.

There is few data on the durability of the repair tissue, there is few data on the nature of the repair tissue, and biopsy that are available, many report

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fibrocartilage, although it has to be said that there is some mention of hyaline cartilage including some Finnish data and including some other articles.

[Slide.]

Periosteum and perichondral flaps will be the first topic. Hoikka, in 1990, studied 15 patients with osteocartilaginous grafts. The sponsor commented on this in the briefing packet. He reported extremely good results in all cases. There were no biopsies initially.

I am sorry, I am going too fast. Let me go back.

[Slide.]

Rinaldi studied 15 patients, and he is the guy that reported extremely good results in all cases, but there were no biopsies.

[Slide.]

McDermott studied 100 patients with a variety of defects including patients with acute knee trauma; 75 percent of the patients at an average of two-year follow-up did well. He did study 24 graft failures, found fissuring, loss of matrix staining and chondrocyte clumping.

[Slide.]

Finally, Homminga, as has been alluded to earlier, studied patients with perichondral strips attached by fibrin glue. Eighteen patients out of the 25 that he studied with

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chondral lesions were free of symptoms by one year. He did do three biopsies, found microscopically that there was a solid core of bone attached to the thick cartilage, and you can read up there what the microscopic data showed.

I want to point out that the predominant tissue was cartilage in all these biopsies.

[Slide.]

Second, abrasion arthroplasty and subchondral drilling.

[Slide.]

Johnson, as you have already heard, studied 104 patients with osteoarthritis, a different indication. Of the 95 patients he treated, 74 were better at two-year minimum follow-up, 15 worse, 7 the same, 3 didn't answer the questionnaire.

He did biopsy at least 8 patients, showed fibrocartilage in most of them. One patient, however, did show some Type II collagen indicative of hyaline cartilage.

[Slide.]

Friedman studied abrasion and debridement in 73 patients with osteoarthritis. These patients had Grade IV lesions, 60 percent showed improvement at 12-month follow-up, 34 percent were unchanged, and 6 percent were worse.

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[Slide.]

Dzioba in 1988 reported a procedure involving drilling and debridement, that in the 65 cartilage knee lesions he studied, following the patients for two years, 69 percent had good outcomes. He followed 42 of these patients for four years and found that they had sustained benefit.

Biopsy, it was a little equivocal and difficult to interpret the paper, but there was some indication that high concentrations of proteoglycans indicative of hyaline cartilage as stained by toluidine blue were evident.

[Slide.]

Next is debridement.

[Slide.]

Sprague treated 63 patients up to 21 months of follow-up with a mean follow-up of 13.6 months; 74 percent had good results, 10 percent had fair results, and 16 did poorly.

[Slide.]

Baumgartner studied 44 patients. As has been mentioned, 50 percent of the patients had good results after an average of 33-month follow-up, others had lesser benefits.

[Slide.]

Finally, lavage. Burman, in 1935, described

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benefits of knee lavage. We have heard today that there are transient benefits that can last for many months. Usually, though, there is no durable clinical outcomes associated with this.

[Slide.]

So, in summary, as I have said already, short-term benefits less than or equal to 12 months are commonly associated with many therapies, and indeed some longer term benefits are also reported, but less commonly.

[Slide.]

Let me speak briefly about the 12-month registry data. As I said earlier, we are very interested in the committee's opinion regarding this.

The sponsor has shown some impressive results on patient improvement, as you have heard, and in our brief review we have only recently received the data. We seem to confirm those in the summary form.

There are significant advantages -- although we still have to do a formal line listing review of those patients -- there are significant advantages to having registry data, as the sponsor has also talked about, two of which I have listed here. You develop prospectively questionnaires, and patients are assessed both before and after treatment, a significant advantage.

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There are some limitations, however, that I wanted to point out. Some of these are similar to those in the Swedish data set. In this particular case, those few patients that have been treated and found that concurrent therapies can exist, and then there is obviously other limitations at this point in time anyway that durable responses are not measured, and while we don't require durable responses for the MAS cell policy document, given that short-term clinical endpoints can be used, certainly durable responses could help assess the overall safety and efficacy of Carticel given that it is meant for replenishment of normal tissue.

In addition to this, there is no arthroscopy data, no histology data in the U.S. registry.

[Slide.]

So given the limitations listed, and despite the results the sponsor has given us, data interpretation in our eyes is somewhat difficult, and its overall relevance to determining the safety and efficacy of the sponsor's product is debatable, and actually I hope we have more of that discussion later.

[Slide.]

I have two final slides on the proposed clinical trial. I am not going to go over this except to say that

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the sponsor has been talking with us over several months about a 300-patient study involving at least three arms, one involving their procedure versus abrasion and microfracture, and they intend to study these patients for long durations with 36-month follow-ups, and so forth.

[Slide.]

Let me point out the issues, though, that I think will need to be addressed by this committee, two major issues in particular. The sponsor has not proposed randomized studies, and they have given you some of their reasons for that, but we believe this is something that certainly merits discussion.

The issue of control arms is something that we have discussed at length with them, and we would be very interested in what the committee has to say about how this trial or a trial might be designed.

[Slide.]

Finally, I have listed four minor issues here, but I don't think that they should be completely ignored - the high dropout lost-to-follow-up rate that is anticipated could be problematic, optimal critical endpoints perhaps need to be defined, the patient population, who should be studied, should there be treatment failures, and so forth, and finally, this has actually been corrected. There is no

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variable rehabilitation program as I understand it today, everybody is going to get the same rehab.

That concludes our presentation and I think we will go to the questions and discussion next.

Thanks.

DR. HANLEY: Thank you.

Committee Discussion

DR. HANLEY: We are now ready for committee discussion. This is a chance for members of the committee to ask questions of the sponsor and their presentation, ask questions of the FDA presenters, information that they presented.

We will have adequate time I believe for rebuttals, if you will, to answers and issues that have been brought up by all parties. We will save an adequate amount of time at the end to address questions that the FDA is proposing to the committee.

The floor is now open for discussion. We would like to have questions for the sponsor initially, and then we will move on the FDA.

Dr. Greenwald.

DR. GREENWALD: I wonder if one of the sponsors could come to the podium.

I find this a little ambiguous and I wonder if the

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sponsor can clear this up for me. I wonder if the sponsor could really differentiate their role in the 153 patient Swedish study by comparison to the 12 month, which was described by Dr. Moscicki.

I wonder if that was part of the GTR research protocol, was it eventually embraced by it, and along with that, I wonder if the question could be answered how then did the two studies differ.

DR. MOSCICKI: Richard Moscicki, Genzyme Corporation.

The 153 patients that are described in the BLA, as I mentioned before, were actually part of an internal review and due diligence effort by the company early on as we began to look. We wished to conduct our own independent assessment aside from Dr. Peterson's own data and review to assure that there is a reasonable independent confirmation of his results.

DR. GREENWALD: So it was a historic comparison?

DR. MOSCICKI: Again, I will say the way we approached this, we asked an independent, and we assume unbiased, contractor to review consecutive charts, to look at all of the patients that were in Sweden during a period up to May of 1995, and we had designed a case record for them to use, but we principally wanted to have an assurance

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of the safety of the procedure, and so that that effort initially went to look at safety.

Now, again, because trying to do what the FDA had done, to glean the clinical status among these 153 patients from the chart alone, we thought was problematic, because we didn't know the patients as well as Dr. Peterson did.

So in order to do this in as objective manner as we could, we then devised the questionnaire, which I think Dr. Lizambri described very well in terms of, you know, we sent it out twice in order to gain as many responses as we could, and so that questionnaire was designed to use a number of different modalities including the Lysholm score as a primary tool to try and assess how those patients were at that particular cross-section of time in terms of their clinical status.

So that does differ from Dr. Peterson's own approach, and I think it would perhaps be more fair to allow Dr. Peterson to speak to his own approach, but we felt that our data would confirm that these patients were doing well and similar to how Dr. Peterson had described them using his own scale.

I think that ends up being relatively confirmed with his more recent analysis using Lysholm score.

DR. GREENWALD: So, in other words, you really

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carried out your own internal analysis, if you will, of Dr. Peterson's data, and it wasn't a GTR-sponsored study, it was just an assessment of Dr. Peterson's investigation.

DR. MOSCICKI: That is correct, and it was sponsored by GTR, we had commissioned that, and I might say that because it was done for our own internal purposes, we used that data for the BLA because we understood that such data would be appropriate and under the guidance of flexibility.

DR. GREENWALD: Could you then describe any differences in the protocol, the procedure, that occurred between the 12-month study, which was conducted in the United States, which is ongoing, and that study, any features?

DR. MOSCICKI: Yes, and I think again, as has just been discussed to some degree, the major difference is the prospective nature. Our analysis, only the questionnaires were prospective, and they only allowed us to do an immediate determination at the time of the follow-up, and we had to estimate baseline values.

DR. GREENWALD: I am talking about the technical carrying out of it, where was the biopsy taken from, where is the periosteal taken from, what was the orientation of the periosteum.

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DR. MOSCICKI: I see. You are talking about the histologic data.

DR. GREENWALD: Not the data. I am just asking you about the conduct of the experiment.

DR. MOSCICKI: All of our histologic information comes from biopsies that were obtained by Dr. Peterson and the group in Sweden. We do not have any biopsies that have been submitted to you from the U.S. population.

DR. GREENWALD: You are missing my point.

DR. MOSCICKI: I am sorry.

DR. GREENWALD: What I am asking you is, was there anything difficult in the surgical procedure, in the technical conduct.

DR. MOSCICKI: I see, I am sorry. No, there are probably not major differences, although I think the data in the 153 patients does, in fact, include an early learning experience by Dr. Peterson in which he was piloting this study, in which I think he did have some early failures which colors perhaps some of the outcome.

MR. SURGENOR: My name is Tim Surgenor from Genzyme. The U.S. registry data is collected from surgeons who are performing this procedure in the U.S. Those surgeons were trained by the company in the procedure. Many of those surgeons actually were trained in Sweden by Dr.

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Peterson and then subsequently in an independent training program conducted in the U.S., but the procedure is meant to be as similar as possible.

DR. GREENWALD: As similar as possible. That was the question I asked you.

DR. HANLEY: A little clarification, Dr. Greenwald. I think we have to differentiate between a retrospective review of cases which have been done somewhere else, a published manuscript which you may or may not refer to a study, and a registry. We are dealing with a variety of different bits of information here, none of which fall into the traditional prospective study that we are used to dealing with. We have to acknowledge that and deal with it forthrightly and as best as we can.

Do you wish to address the U.S. study?

DR. GREENWALD: Essentially, you answered the question. The surgical procedure and the conduct of the procedures were essentially identical.

DR. MOSCICKI: That is correct.

DR. GREENWALD: That was my question to begin with.

DR. MOSCICKI: I am sorry, I thought you were talking about methodology of data collection.

DR. GREENWALD: I have a question as regards the

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12-month contemporary study that is ongoing.

MR. SURGENOR: Maybe we should refer to that as a registry.

DR. GREENWALD: A registry, fine, let's refer to it as a registry then.

My question along those lines is we didn't have the benefit of seeing that data as part of our review, but I would like ask -- it was Dr. Micheli -- he indicated when he spoke that there were 30 reoperations and 2 retrievals, and the question is was tissue retrieved at that time?

DR. MOSCICKI: No, unfortunately, we don't have the tissue from those implant removals.

MR. SURGENOR: The 30 reoperations were not tissue retrievals, if that is what you mean.

DR. GREENWALD: But you went in, I assume when you say you reoperated. Was any attempt made to assess the quality of the repair? I mean, for instance --

DR. MOSCICKI: Unfortunately, whatever information that might have been gleaned by those orthopedists was not put into any kind of categorized form, and so we don't really have any of that information in our own database.

MR. SURGENOR: There are several surgeons here today who may have done those procedures, but that would be purely anecdotal observations.

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DR. MOSCICKI: That is correct.

DR. GREENWALD: It would have struck me that that would have been a logical request on the part of the corporation to ask those surgeons, if they did go in and reoperate or did retrieve or remove the two patellas, that certainly tissue samples would have been taken and an assessment of the quality of the articular cartilage, the structure.

DR. MOSCICKI: I think that is a good suggestion for the future. We will try and make all of our surgeons aware, but the truth is most of these things occur, and then we hear about them afterwards when they are reported to us, and then we diligently list those as adverse events.

Some of these events involved Dr. Tom Minas, and he is here and perhaps we can ask him to comment.

DR. MINAS: I am Tom Minas from the Brigham and Women's Hospital.

In my own series of 37 patients to date of cartilage cell implants, I had 14 complications in 12 patients, and the complications were related mostly to hypertrophy of periosteal edges with symptomatic catching or arthrofibrosis in the joint after arthrotomy, and I had 1 patient with a DVT after tibial osteotomy with cartilage graft.

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In those relooks, arthroscopic relooks, those 14 reoperations, the tissue that I basically took down was scar tissue within the joint. Reassessing the chondral grafts at that time revealed that there was a fill of the defect and the hardness of the tissue fill depended on the time after the implantation, so that a trend that I found was that early on there was a very soft tissue fill with incorporation to the surrounding cartilage edges of the graft, and that the subchondral bone integration was not evident until about six months afterwards when the graft would still have a soft texture to the surface, much like putty, you could indent it, but it no longer would move along the subchondral bone, and a rescope at nine months demonstrated that the tissue was hard and smooth as the adjacent cartilage when probed with a nerve hook.

I had one of my patient's four grafts delaminate, and we retrieved that specimen at three months and analyzed it histologically.

What we found was that at the surface of the graft or the periosteum, it appeared to me that the graft was a composite consisting of periosteum plus repair tissue that was deep to it. The surface of it had very much a fibrous appearance.

The deeper portions had evidence of a

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fibrocartilage type repair, and the deepest portion of the graft, which was still adherent to the bone, had chondrocyte with hyaline matrix, and we stained those for Type II collagen, and as early as three months there was large amounts of Type II collagen, large amounts of safranin O staining proteoglycans, and it appeared to me that the graft repair was from deep to superficial and that the periosteum was part of the repair process.

So there was just the one entire graft that delaminated that we could look at histologically. Of the repair tissues that had catching, of which there was six, with periosteal hypertrophy, what the graft edge looked like, it was prominent and hypertrophic, and overgrown to the adjacent surface.

In a few of those, I just got sharp arthroscopic scissors and just snipped it flush, and took that tissue to examine, and it basically just looked like a periosteal fibrous layer that had hypertrophied. There was very little in the way of any cartilage repair at those junctions. The symptoms of the patients resolved with just trimming the graft flush with the surrounding cartilage.

So the only retrieval we had was the one complete, where part of it came off, and I just peeled the entire graft off. The part that was not attached to the

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subchondral bone was essentially fibrous tissue, and the portion that was well attached had good cartilage deep to it, and the superficial portion appearing like just fibrous periosteum.

DR. GREENWALD: Thanks, Tom. I have just one final question that you could answer for me, and it is a curiosity of mine. I would like to know what is your rationale for the orientation of the cambium layer being now faced towards -- if I have got it correctly -- facing towards the subchondral plate. Can you kind of explain that, please?

DR. MINAS: Sure. The technique was initially devised by Dr. Peterson, so the initial rationale was -- the same question I asked, because in the published experimental work, the cambium layer was always facing up, and in my perichondrial graft experience, the cambium layer was always facing up and the regenerative cells were always from that layer, and they grew into the joint -- so what it appears to me, and I think Dr. Lyndahl can answer this question more eloquently -- is that I think there is a paracrine effect of the cambium layer of cells along with the chondrocytes, and when we look at our retrieval, both human retrieval that I just mentioned, it appeared there was colonies of cells that were up against the undersurface of the periosteum, but in

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the animal model that was done in the canine model, what we found was that when we had the beta-gal-labeled cells to the undersurface, we saw the most growth was along the margins, the base of the bone, as well as the underside of the periosteum, so I know Dr. Lyndahl has done more work to evaluate what he feels is a paracrine effect of several interleukins and TGF beta from the periosteum to the cells.

That appeared to be the clinical situation from the retrieval we looked at.

DR. GREENWALD: Thank you.

DR. MOSCICKI: May I make one small comment in regard to your earlier question regarding why the company also doesn't have all of this information. We don't have IRB approval or informed consent in order to get such information at the present time.

DR. MINAS: In the study that I did at the Brigham, we have an IRB approval for biopsies at two years, so when I speak with the patients, we are not doing any biopsies earlier on, so that we do not jeopardize the regenerating grafts as they are still soft.

One thing I noted when I was doing the debridements of the hypertrophic edges, if you put a motorized suction device powered shaver, you really could almost pull the whole graft right off, so that I think

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really trimming it with sharp dissection in a protected arthroscopy blade is crucial, and my concern was to biopsy it at early times I might jeopardize the graft.

DR. HANLEY: I think this is all getting at a critical question, and that is that in the submission and in the discussion, the vast majority of the information provided is from Sweden. The information from the U.S. registry is incomplete at best, many anecdotal comments, experiences relayed.

The information presented today by Dr. Micheli is different from what was submitted and a little more elaborate probably. We have no histology, and we have an issue for the committee here. I am not sure we can resolve it in this discussion, but I would like everyone to think about this. We are dealing with the scientific part, if you will, from elsewhere, and the information that we traditionally employ here that isn't as good for the reasons that we have all discussed, and it presents issues that may or may not be resolvable for us.

DR. MOSCICKI: May I comment for one second on that. The U.S. registry data is different in that actually it is more rigorously collected, you know, that there is a prospective assessment, as well as periodic follow-up assessments on the patients.

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So to a very large degree when you look at a group of patients out over one year, we have almost complete records as far as a prospectively determined case record form essentially and collection of that information and interpretation in a way that does allow us to do statistical analyses.

DR. HANLEY: A clarification, Dr. Siegel?

DR. SIEGEL: Yes. The Agency has considerable experience with foreign data. We do accept it and have, in fact, an agreement I signed yesterday in Tokyo is one called ethnic factors and the acceptability of foreign data.

European data in particular has often been utilized. The Agency relied heavily on the European data, but I want to speak a bit about how we have used the U.S. data, in part because that was the bulk of the data available up until rather recently, but also because of our determination that the six-month and now 12-month follow-up on the U.S. data places a substantial limitation on the ability to make determinations about outcomes since as noted by many of the speakers and sponsor and elsewhere. There are a lot of things that one can do without giving cells, even lavage and debridement give outcomes that look pretty good in that period of time, and it is the durability that is the key.

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So the biopsy data and the durability data caused us to look more closely at the European data. We did look at the U.S. data and compare it to data -- although not presented -- compared it to data gathered in about the one-year window in Sweden.

Now, the Swedish data were not prospectively planned, so there weren't the same end points and there weren't the same time points, however, it is our general assessment given the limited ability to do that, but it is our general assessment and one of the things we did want to check for was to see whether the U.S., at least to the extent it has been acquired so far, to make sure that the U.S. data was consistent with outcomes in the Swedish data, and I think that we can say that is our finding.

DR. HANLEY: Very good. Thank you.

Dr. Kuettner.

DR. KUETTNER: My name is Klaus Kuettner and I am from Chicago.

I don't want to pick up so much on the data, but rather on the differences in methodologies between the Swedish approach and the U.S. approach.

The one is when you isolate the cells, the chondrocytes, you interject there a phase of cryopreservation, and for those of us who are working for

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decades with chondrocytes, chondrocytes are very difficult cells to handle, and so I wonder if you could give us any comments about the cryopreservation, the viability after the cryopreservation. That is question one.

The second one is in the Swedish study, after the chondrocytes have been isolated, they are cultured for expansion in human serum. Now it is fetal calf serum. Again, fetal calf serum is very different -- the way I understand it at least in your protocol -- fetal calf serum, you can have different batches of fetal calf serum. Some of the fetal calf serum is just fantastic for chondrocytes, other fetal calf serum batches are very poor for chondrocytes, so you are introducing an additional variable which, in my eyes, is a little difficult to overcome.

Finally, you are just talking about a morphological identification of the differentiation, and I would like to have a little better definition what is a morphological identification of the differentiation as it is in your protocols. I have three questions basically.

DR. MCPHERSON: In terms of freezing, you are right, Dr. Kuettner. The process we utilize doesn't routinely involve freezing cells after primary expansion. That was required mainly because of scheduling issues and issues related to reimbursement.

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Now, to evaluate the effects of freezing on chondrocytes, we have done a number of evaluations. The first is to look at cell viability, and cell viability coming out of a freeze is very high, greater than 80 percent.

The second point was we have looked at the capacity of a number of cells, a number of preparations or strains for the capacity of these cells to redifferentiate using soft agar as a means to establish redifferentiation as judged by Type II expression, aggrecan expression, and so forth, and we have validated in 24 different strains the data which we have submitted to the FDA, that these cells, following freezing, these strains have similar capacity to unfrozen cells in terms of their ability to redifferentiate.

We have also looked at number of doubling times to senescence as a means to evaluate the effects on cell functionality, if you will, and cell proliferation. We have also looked at proliferation rates. In our experience, again with 24 different specimens, we have not seen a significant difference either in the rate or proliferation or the average time to senescence from these cells.

These cells were derived from patients ranging in age, I believe, from about 15 through 54, so we have looked at a broad range of specimens or samples in this validation,

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the data of which has, as I have said, been submitted to the FDA.

Now, in terms of fetal bovine serum, we did change the fetal bovine serum primarily for commercial feasibility reasons. Trying to obtain autologous human serum in the way that we produce these cells would have been extremely difficult.

Beyond that, we actually saw more reproducible cell proliferation rates with cells cultured in fetal bovine serum than we did in autologous serum in general.

The issue of variability of different fetal bovine serum lots in terms of cell redifferentiation, we have reported, and what we have seen is that if you evaluate cell redifferentiation in a suspension culture system, there is variability in terms of time to redifferentiation as a function of different serum lots.

Recent experiments indicate that redifferentiation is driven by a combination of TGF beta and insulin-like growth factor, and in these different preparations of fetal bovine serum that we have used, it appears that variations in the level of free IGF is responsible for these variabilities in fetal bovine serum.

But the point is fetal bovine serum in the production process is used to stimulate proliferation on

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plastic. The issue of suspension culture effects is a separate issue that is unrelated to the process.

Now, in terms of morphology, in the BLA submission we have presented information that if you look at the general morphology of articular chondrocytes that have been enzymatically release from articular cartilage, you can see some degree of variability in terms of the morphology of these cells.

Most of the cells have what we call a typical appearance. There are cells that are more dendritic in their morphology. We have concerns that in the situation where we have a dendritic morphology, they could be atypical cells, cells derived from osteoarthritic kinds of situations, and for that reason we have trained technicians to understand and be able to identify or classify cells whether they are more normal-looking chondrocytes or cells that would fall into what we call this atypical category.

It is as simple as that. I mean it is an issue of seeing cells at times in certain patients that look atypical. Actually, over time, the number of those cells seem to diminish. We do not know whether it is a consequence of reduced proliferation rate simply being overgrown by the more traditional kinds of chondrocytes, we do not know. We are working on that right now.

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As you know, it is difficult to identify dedifferentiated chondrocytes immunologically. We have discovered based on RNase protection, that these cells do continue to make small amounts of aggrecan, which would be unique to chondrocytes, and we are currently trying to use phage display antibody production technologies to produce specific antibodies that would allow us to identify chondrocytes in a dedifferentiated state.

DR. KUETTNER: I would add a comment to what was said this morning, that Type X collagen is a marker for growth plate calcification. Type X is a marker for hypertrophy of chondrocytes. Type X has been shown by several groups now as a marker for osteoarthritis, and not necessarily for calcification, so that that was a little misleading this morning. I am sorry to correct you there.

DR. McPHERSON: You are absolutely right. If I said that, I meant that it was a marker of chondrocyte hypertrophy.

DR. KUETTNER: Hypertrophy rather than calcification.

DR. McPHERSON: You are correct. I was thinking of it in the context of endochondral bone formation and chondrocyte hypertrophy associated with that situation.

DR. KUETTNER: Just to follow up, when you take

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your dedifferentiated chondrocytes, which you have now increased by a factor of x, whatever it is, and before you reimplant them in the patient, do you in every case do a testing if they are now capable of being redifferentiated to chondrocytes, or is it just an assumption from past experience?

The reason why I ask, because your agar system is very good, but may not be absolutely necessary because you can just do these spot cultures of very high density, and immediately any cell which was originally a chondrocyte will go back in the form of a chondrocyte, and it is easier system to test this.

DR. McPHERSON: The answer to the question is no, we do not analyze the ability of every patient's cells to redifferentiate before release. In our experience, in suspension culture, it takes a minimum of a week to see redifferentiation based on RNase protections kinds of analysis of gene transcription induction.

We use alginate for those kinds of experiments because, as you know, it is very difficult to do RNA isolations from agar. In our experience, it takes at least a week to get a strong signal that is indicative of induction of Type II collagen.

It really is not feasible, we believe, for us to

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analyze every patient for the capacity to redifferentiate. What we have done is, as I have said, we have validated that our process provides the opportunity for these cells, or does not impinge or handicap these cells' capacity to redifferentiate.

We have a reference strain that we use on a regular basis to ensure that we are not making unknown changes to the system.

DR. KUETTNER: My main concern was when I read it and when I heard it today again, you are focusing on the appearance of Type II rather than the disappearance of Type I. That is, in my eyes, the critical approach. You say that the cells which have been dedifferentiated into a fibroblast cell, and they are coming back up to be redifferentiated, they should cease to make Type I, and that can be done by in-situ hybridization, and it is a very easy and fast method.

DR. McPHERSON: Sir, we have looked at down-regulation of Type I collagen from adult human chondrocytes over time, and in our experience, Type I collagen expression in suspension culture does not cease for at least five weeks, four or five weeks, it is not instantaneous, just as up-regulation of Type II is not instantaneous.

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So, it is a time course of redifferentiation that takes several weeks to observe. Now, in the cultures that we use on a regular basis with serum as a means to stimulate redifferentiation, we do see this down-regulation of Type I collagen. Interestingly, if you put the cells in defined media and give them on TGF beta and IGF, it takes much longer, as you might predict, for the Type I to go down.

DR. KUETTNER: Thank you.

DR. HANLEY: Thank you. Dr. Auchincloss.

DR. AUCHINCLOSS: This is Dr. Hugh Auchincloss speaking. In my view, the most significant feature of the FDA presentation was the poor correlation between the functional outcome and the presence of hyaline cartilage, and I wondered if the people from Genzyme would like to comment on Dr. Poole's data in general pathologically.

DR. MCPHERSON: First of all, we would concede the quality of the slides that were presented to the FDA were not optimal. I think Dr. Poole emphasized that five or six times. These were not our slides, they were the slides from Dr. Lyndahl's lab. They were done in a laboratory environment, a research laboratory environment, they were not done professionally in a clinical lab.

In terms of the differences in interpretation, we combined the specimens that showed either large amounts or

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predominantly hyaline cartilage with those that were completely hyaline cartilage because we believe that this is a unique picture of histological repair. You do not see hyaline cartilage generally following drilling or abrasion or those kinds of procedures.

So we combined the specimens that were broken out by Dr. Lizambri which showed no correlation, and actually combined the specimens that were either completely hyaline cartilage or predominantly hyaline cartilage, because we were asking the question is there a correlation between unique tissue histologically and clinical outcome, and we believe there is.

Now, I must say that the report that we had from Dr. Poole dated January 21st spoke to the issue that he mentioned in a very forceful way, and that was that patients there was subsequent follow-up on, there was evidence of degeneration.

Now, in the original report that he had we were puzzled by the fact that although his narrative indicated that he believed degeneration was going on, his scoring system indicated that in Patient 1009, the score did not change, it was a 4 and stayed a 4, Patient 1012 went from a 4 to a 3 several years later, despite the fact that the said there was degeneration. Then, one of the patients, No.

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1011, was originally a 5 at original observation, and then several years later was a 2. I think that Dr. Poole mention in the report that he believed that patient had improved.

On February 21st, we had a conversation with Dr. Lizambri about this because we were puzzled by the fact that the grading score which, as Dr. Poole has mentioned, lower numbers is a better score, did not correlate with his narrative. Now we understand that on February 25th, the scoring system was changed.

Unfortunately, we do not have a copy of that revised report, so we did not understand what Dr. Poole was referring to here in terms of defibrillation and the fracturing, and things like that. We are in an awkward situation because we did not have the final report after it has been revised following our conversation with Dr. Lizambri.

DR. POOLE: In response to that, I had a consultation with Dr. Lizambri following on his consultation with you with respect to the apparent inconsistency, and I expressed the fact that the grading system, as I said today, is a very arbitrary grading system.

What I hadn't taken into account in the initial report was the recognition and classification of fibrillation split into the mid and deep zones, so I added

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that in, and the gradings changed because that was a feature of the follow-up in some cases, that there was fibrillation in mid and deep zones, in the initial grading system that wasn't included.

So I revised the report to take consideration of that because that was obviously a factor that I should have initially considered, and therefore, I considered it in the revision. I am sorry that you didn't get a copy of the revision because it was submitted and it is a fair comment.

DR. McPHERSON: Sir, there is one point that perhaps someday you and I can talk about, and that is, you know, the orientation of these specimens, I think you mentioned it is difficult to understand what the orientation is, and I am not sure that I completely agree or our people completely agree with the conclusion that this is evidence of fissuring or fracturing.

Because of the quality of the slides and the ambiguities about orientation, I think that you and I could have a conversation about this and perhaps understand where each other is coming from. That is one point.

The other point is I would only emphasize that no one really has had the opportunity to study cartilage repair in the way that we perhaps will in the future. So it is difficult to ascertain, I think, the difference between

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repair and degeneration.

For example, in your notes you talk about cloning, and you are absolutely right, cell proliferation is a hallmark of degeneration. On the other hand, cell proliferation could, in the reparative process, also be a hallmark of repair.

So it is looking at a 100 cc glass that has 50 cc in it, and it is difficult, with the absence of other information, to know whether it is half full or half empty.

DR. POOLE: I agree with your comments. I think some of the problems we face in assessment related to preparation of the material -- and we all agree that we need to improve it -- in my assessment of the cloning and the changes that I saw in the cartilage, these were made in relationship to degenerative processes that we have had a chance to look at in human articular cartilage.

You are absolutely correct, because this is really the first time we have ever had a chance to look at these processes and changes in human cartilage, so I relate to what we can look at, and so I relate to things like osteoarthritis and degeneration with aging, so I have to relate to human changes because I think they are the most appropriate, but it is a fair comment.

But when I look at it and when we do the

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follow-ups, we need many more follow-ups, because these are terribly important. When we don't see improvement on the follow-up, that convinces everybody, then, I think we have concerns about whether or not we are looking at an active, ongoing repair process if we don't see improvement on follow-up. Clearly, we need many more specimens.

DR. McPHERSON: Sir, may I ask you just one question about your report? It is just a very brief question. In your report, you spoke of a number of issues, limitations of the data, this issue of degeneration, and in the last sentence you say, "The results are far from perfect, but they do offer promise for a new valuable approach to management of joint injuries of this kind."

Sir, could you explain to me what you meant by that?

DR. HANLEY: Let's move on with the panel's questions. I think we are here to ask you, the sponsors, about the information you presented, not the reverse.

Dr. Sledge.

DR. SLEDGE: Thank you.

I think to some extent, some of the confusion comes about because, at least in my view, we are missing a point here, and that is the goal of this treatment, as I understand it, is to restore a functionally sufficient

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tissue. Whether it is hyaline or not is not really the issue, and therefore, it is no surprise to me that there is so little correlation between the histological appearance and the functional scores.

Let me expand on that a little bit. Hyaline cartilage merely refers to either the histological appearance or to the chemical composition. It does not address the three-dimensional structure, which is what gives the articular cartilage its mechanical abilities.

One way to get at that, you mentioned in some of your studies, was use of indentation, which measures not only the chemical content and composition, but the three-dimensional structure to give it certain resistance to compression.

My question then is in order to better understand the relationship between the regenerated tissue and durability and function, why not routinely employ indentation as a noninvasive way of assessing the integrity of the tissue?

DR. MOSCICKI: Yes, Dr. Sledge, I think you are absolutely correct. Our interpretation of hyaline was that we saw, in fact, a staining pattern that we felt was very consistent with the hyaline structure in terms of proteoglycan content and uniformity of staining.

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I think the correlations actually do hold up if you look at it from that perspective in relationship to the type of outcomes and the way that we had determined those outcomes.

I think even if you look at Dr. Lizambri's analysis, I mean he broke out the clinical responses into three different groups, and that included a large group of some improvement which covers a very broad category. I think Dr. Lizambri would be the first to say that, because at the very far end of the spectrum, as he pointed out, the patients who had a return to full activities was a very rigorous definition of an excellent outcome, so that when you combine those two groups, and if you looked at the presence of the appropriate staining patterns, I would suggest that that analysis would probably better show the issue of correlation.

In terms of the indentation, we think that is a wonderful idea to do. Unfortunately, the tools for doing that have not been generally available. The only readily available tool to the orthopedist has been a simple probe and with a subjective determination of response to that probe.

However, Dr. Peterson and Dr. Lyndahl, as you heard earlier today, have had the opportunity to use an

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indentation instrument developed in Finland. Now, this instrument has not been widely used, and so they were I think fortunate in order to have that ability.

As you saw from their presentation earlier today, I think it is fairly impressive that there was a correlation when one looked at the indentation measurements in relationship to the determination of the presence of hyaline tissue using the definition that we had, and I think that you, in fact, have just proposed for hyaline tissue, and there was a dramatic difference, in fact, a significantly different result when those specimens that had fibrous repair were compared for their indentation.

So I hope that perhaps such information can become more available when these instruments become more available. Perhaps on that I might add to the U.S. registry, why we have restricted ourselves currently to clinical outcomes. In general, it has been because in a general atmosphere, such as a registry, it has been very difficult to enforce reoperative second looks in order to gain some of that type of information.

DR. HANLEY: Dr. Sledge.

DR. SLEDGE: Just two quick follow-up questions.

Again, it is not surprising that it is better to look hyaline than not look hyaline. I am suggesting that is

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not a sufficient degree of sophistication to predict durability, and indentation has been around, to my knowledge, for 15 years. It is not a new discovery, and its correlation with the chemical composition has been known for that length of time.

But with regard to the clinical information, I am a little surprised that you have chosen in the registry to use only one validated instrument, the SF-36, and as I understand it, the Modified Cincinnati and the other scales, and the Lysholm, are, to my knowledge, non-validated instruments.

Is that correct, and if so, why wouldn't you use a musculoskeletal-oriented validated instrument, such as Womack or some other scale that has been widely validated?

DR. MOSCICKI: Are you speaking about the comparative trial or the registry?

DR. SLEDGE: The registry.

DR. MOSCICKI: In the registry, after much discussion with a number of orthopedists, they had proposed to us this use of the Cincinnati Knee Score developed by Dr. Frank Noyes and modified to reflect cartilage.

I think that the Womack score might be certainly of interest in supplemental, but it is developed for patients with inflammatory diseases --

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DR. SLEDGE: No.

DR. MOSCICKI: Okay. Then, I can be corrected on that, I certainly would enjoy hearing more, but I think Dr. Minas would like to address that, as well.

DR. MINAS: I was consultant to the development of the industry. At the time when the other surgeons were discussing this, those exact questions were asked. The SF-26 is a validated instrument, the Womack is a validated instrument, and the Knee Society score is a long-term knee score, that was well known to the orthopedic community, as well as the Noyes Cincinnati score.

As this particular injury pattern is quite common in young individuals, most of the treating surgeons have a sports medicine background, and they felt most comfortable with the Cincinnati knee rating score over the other scores, which tend to be used more in an arthritis population.

In my own ongoing study, we have used the SF-36, the Womack, the Knee Society score, as well as the Cincinnati knee score, and found that to be extremely sensitive and demonstrating very large effect measures in a validated instrument.

So I think we are talking about using that in the comparative study, although it is not in the registry, that the SF-36 will be part of the comparative study along with

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the Cincinnati knee score, so that both a well-recognized health science utility instrument, as well as a sports scale, will be used.

I think the Musculoskeletal Society score from the Academy will be involved, as well.

DR. SLEDGE: Thank you.

DR. HANLEY: Dr. Tomford, do you have a question?

DR. TOMFORD: Yes. My main concern about this is that this is not articular cartilage, that it is a mixture perhaps of fibrocartilage and articular cartilage. It looked to me in the slides that Dr. Poole showed that the periosteum does play a role in this.

Why are you eliminating the obvious choice of using periosteum as a control in your study that you have proposed?

DR. MOSCICKI: I will come back to that -- well, let me proceed with that. We discussed a little bit earlier the rationale, and this was discussed with our investigators, and it basically boils down to the fact that periosteum alone, without any penetration of the subchondral bone plate, has not been demonstrated to be of benefit to patients.

In that regard, it seemed inappropriate to all concerned, after that discussion, that one might subject a

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patient to the open arthrotomy and its risk, as well as to the six month of rehabilitation necessary for what essentially could turn out to be a sham operation, which there hadn't been very good evidence to support that these patients could expect a reasonable benefit after taking that kind of risk.

I think that is really what in the end it boils down to. If one were to entertain the concept of using Dr. O'Driscoll's technique as something approximating a periosteal patch, we thought, and our investigators also thought, that that too would be problematic in that that has been a difficult technique. I think Dr. O'Driscoll would say so himself.

The results that he presented recently perhaps go along with that, and the consistency has been a persistent issue surrounding that technique.

DR. TOMFORD: The results seem to be poor in the patella and other areas.

Is the BLA confined to femoral condyle defects or does it include other areas?

DR. MOSCICKI: No. The indication that we have proposed for the use is strictly on the femoral condyle. That is what we are looking for, for approval.

I think Dr. Peterson might argue that the early

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data on patella did not look good, but his most recent data in fact is encouraging. However, the data that we have submitted, the data that we have reviewed, the data that I think FDA has reviewed has been largely aimed towards the femoral condyle in terms of providing support.

DR. HANLEY: Dr. Rangaswamy.

DR. RANGASWAMY: I have three questions. Given the endpoint of 6 and 12 months, which is what we are looking at, and the controversy and problems that were highlighted by the NEJM, which is really incomplete, and had some major flaws, it is somewhat strange that you would not have established the well-designed trial that you now want to do at that time, which is about two and a half years ago. That was one question, I am curious why you all didn't think of that.

The second is why was an animal model not used to provide long-term histologic data. That is what everybody keeps talking about.

The third is would you concede that at this time, based on the information that you have presented, that has been discussed on the cartilage cell transplants, that that operation is really no better or worse than the other treatments given the 6-month and 12-month data and given the review of the literature that was done earlier, if you look

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at all of them at 6 and 12 months, is this really any better or is this about the same as the other one?

DR. MOSCICKI: I will attempt an initial discussion in regards to the clinical trial. I think Dr. Peterson and we would all agree that the New England Journal of Medicine article was intended as an expression of the initial experience and the excitement that there was, that this appeared to be an approach that had merits, and none of us felt that this was the end-all in the definitive article.

Yet, our conversations with many orthopedic surgeons, as Mr. Surgenor had opened up with, encouraged us very much so to make this available to those orthopedic surgeons who were desirous of trying to use it. It was not regulated, and so there was no, at that time, need for such a trial.

Such a trial is also a very expensive undertaking. We estimate that the current trial is going to cost around \$6 million, and we felt that it would be a good initial approach to rigorously collect the clinical outcome, which has never been done before, in the manner that this registry does in the field of orthopedics for these types of procedures.

So, we instituted at that time that it was made available a registry to collect these outcomes and observe

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them over time as rigorously as we could. It became apparent to us as we talked to an increasingly larger audience of orthopedists that it would be useful for orthopedists to have a comparative trial ultimately, and I think the FDA would probably agree, that we would like to see that over a long period of time, to be able to have something at the end of that, to not just look at the benefits in relationship to the procedures alone, but in comparison to other procedures, and I think third party payers will also find that very useful.

So that is how this evolved in terms of our thinking.

DR. RANGASWAMY: Even if this was an unregulated product at that particular point in time, the question comes in, since you obviously spend R & D money on this to do it, and you were looking to get this data because you wanted to get it accepted, that was only my concern, that it was a premature publication, would have done better to have been looked at much more critically and then presented.

DR. MOSCICKI: I would like Dr. McPherson to comment on the histology question that you asked.

DR. McPHERSON: In terms of an animal model, I think you were proposing or asking the question why didn't we evaluate this in animals before commercializing it for

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human patients.

First of all, there is no well accepted animal model of cartilage repair that we know of. We have looked at rabbits. We have recently concluded a study actually with Dr. Mencken's group looking at healing in rabbits. Drs. Peterson and Lyndahl and Grandy have already published data in rabbits suggesting a positive effect of cell implantation and repair, but the fact is rabbit cartilage is extremely thin, and trying to sew periosteum in place and get a reproducible result is very, very difficult.

So we did an experiment in dogs, 24 dogs, it was about a \$350,000 experiment, and that experiment ended up showing us that, first of all, in dogs, the cartilage is quite thin, as well, particularly compared to humans. It is about 0.6 mm in thickness to 0.8 mm in thickness.

The dogs have a significant degree of spontaneous healing that we didn't anticipate. Older dogs in particular routinely develop arthritis, and it appeared that this surgical procedure that we utilized accelerated that process because all of the dogs we treated developed degenerative joint disease.

So now we are working on goats, and we have lots of goats in our animal facility, and we are trying to devise a way to control the motion of these goats because

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rehabilitation in a goat is very challenging. They like to stand up and look all around, and that doesn't happen with a human obviously.

Dr. O'Callahan, our veterinarian, is developing a number of splints and restraining devices. The bottom line is it is very difficult to develop an animal model of cartilage repair. I do not believe that there is any generally accepted model of cartilage repair, and therefore, to treat patients -- I am sorry -- to work everything out and have definitive data in animals before we treatment patients given the Swedish experience seemed to us to be unreasonable.

I would like to make one other point as well, and this was brought up at the Academy meeting a few weeks ago. Even for cutaneous wound repair, human cutaneous wound repair, there are really no good models of repair. Domestic pigs are often used.

Our other autologous-based cell therapy, which is called Epicel, which is a keratinocyte grafting technology, that is used to treat severe burn victims, and we have treated well over 1,000 patients in the last few years, it is a life-saving procedure, yet if you tried to do this procedure in a pig, i.e., culture pig keratinocytes, get them into a graft and transplant them, the majority of the

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time the graft won't take, and we are only now beginning to understand why that is.

But the point is animal models of wound healing in general are difficult to develop and validate and oftentimes are not very predictive of what happens in humans.

DR. MOSCICKI: I would also like to comment on what you said about the 6- and 12-month registry data. I think that is a very important point that you make and an interesting one.

I think, first off, the comparison to the literature that you refer to I think is extremely difficult. It is problematic because much of the literature doesn't involve the same patient population. If you look at some of the lavage data that was presented, it is not really the same population that we are talking about.

So to try and make these percentages and put them up side by side and say anything about it, I think is extremely difficult. Rather, I think that the value, and the value that we really propose for that information to you today, is that this provides evidence that these patients are better, that simple. These patients are statistically better by a number of different measures. Whether or not the Womack score, these are reasonable scoring systems, we think, in order to measure that kind of benefit.

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Could such benefit perhaps be equal to that of alternatives? Maybe in that short-term period. I won't argue with anyone on that issue, but that is not the point that we hope to make here. We hope to make that there is, in fact, benefit and that is consistent with what the MAS guidelines have, in fact, suggested, that there be evidence of short-term benefit.

DR. HANLEY: Thank you.

Dr. Siegel, clarification?

DR. SIEGEL: I would like to clarify that. I received a number of questions during breaks about this issue, and always prefer everything to be in public, and where one or two people were confused, there is probably a lot more confused.

When I initially addressed the issue of choice of control groups and comparisons, I did it in the abstract. We had yet to hear about this product and this disease. I think at this point it would be helpful if I gave at least our present perspective on how that would apply to this disease.

The product that we are seeking approval for here is a cellular therapy, but of course, it is administered in conjunction with surgical procedure, sometimes follow-up surgical procedures, and an intensive postoperative

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rehabilitation course.

The best way to determine the contribution of the cells would be to have everything the same here but for the cells. That experience does not exist. I hope to make it clear that the lack of existence of that experience does not or should not mean in our minds that we then should just go home, particularly given, as has been noted here, the way this product has developed, and our attempt to see, not so much -- and I want to make this clear, too -- not so much to apply different standards of efficacy, but to look carefully to see whether exploring the various types of data we have available, what can be determined from those data.

So what does that mean regarding comparisons? Well, on the one hand, we have said, and made clear, that this therapy need not be superior to other effective therapies, but as I noted before, it is also important to bear in mind that it has to be shown to be effective.

Now, there are two ways that therapies are typically shown to be effective, one much more common than the other in terms of Agency review. The most common way by far is by showing it to be superior to either no treatment, placebo, sometimes a low dose of the same therapy, sometimes another active and accepted therapy, or even an experimental therapy if it is thought that that one has little likelihood

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of doing harm. Clear-cut superiority to any of those would establish that a drug has an effect.

A second, less common way is by showing that a drug or biologic has equivalence to an active therapy. This is less common because it is a very difficult proposition. For one thing, one has to be certain that you have an active therapy of known efficacy. It has to be of known and quantifiable efficacy, and it has to be of reproducible efficacy, one that you know if you compared it to a control, it would have a quantifiable and reproducible amount of efficacy.

The reason that we have those requirements -- and these two, I discussed historical controls, but these sorts of active control comparisons have also been greatly discussed and negotiated -- and the reason those requirements are there is because when you compare to an active control, therapy as an endpoint, you determine of course the difference between the therapies and a confidence interval.

You set a limit. If you are not requiring that the drug be superior to an active therapy, you set a limit to how much inferior you need to exclude, which is to say your null hypothesis is no longer that they are equivalent, but that it is not substantially worse than, and you set how

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much worse than the active control therapy, the confidence interval can extend to, and you are still comfortable that you have shown an effect of drug.

To set that limit of how much worse than the active control therapy, a new therapy can be, you need to know how much worse the placebo would be because, after all, if drug is similar to an active therapy within a range that is so broad that it includes the entire effect of the active therapy, then, your drug may be similar to doing nothing. That, of course, does not establish efficacy.

Similarly, there are some effective therapies that are hard to reproduce. In some studies they work, in some studies they don't, and if you compare to an active therapy in that sense, and you are not sure that on the basis of the comparison that that study worked, it is hard to establish efficacy by comparison.

So what we are looking at here, then, is there is not a situation where one needs to be superior to an active therapy, but there is a situation where we are looking for evidence that the treatment itself is effective.

Now, it is very difficult to know exactly what to compare it to. As we have heard, the data just absent the cells, but with the flap, and with the flap used the same way, without abrasion, the same orientation, and in the same

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patient population are very rare.

We have looked somewhat to debridement and lavage. Since debridement and lavage are part of this procedure, we think that debridement and lavage data are important, and we would think it important that this therapy be better than that as to add cells to debridement and lavage, if it is no better, it would be of questionable efficacy.

The data you have heard regarding debridement and lavage, I would have to agree with Mr. Moscicki, much of those data are in arthritis patients. It is hard in this sort of historical database to get the type of -- I noted in talking about historical database, you want a disease with a predictable and consistent course, and you want a comparable population that is comparable by baseline -- I think in part because of the way the drug was developed, but also just in part because of the complexity of the type of treatment, the issues you have heard about, would anyone do the same thing without the cells or whatever.

The data are not of the type that we would like to look at, so we are asking the committee, with that in mind, to provide whatever help in terms of making a determination of the data we have.

DR. RANGASWAMY: Dr. Hanley, could I ask him a quick question? The issue is not that we are comparing it,

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because you can't compare them. There is a problem when you look at any retrospective study. I think part of the problem here today is the fact that you are looking at retrospective data, and there is always flaws and limitations in it. Even though you can't compare it, the issue really comes in, even though you look at each one in a separate box, open each door and look at each methodology, does it function, is it good, is it not good.

I am not saying to compare whether this is better than that. I don't think you can do that at all. But there is another thing. I have talked about different other things, but here also we really don't know a lot about the natural history of this particular thing, because you only see the patients who come in. You also don't know about the number of patients who may have similar lesions who just have not shown up or who have elected not to get something done.

So there is a whole host of information, not them, nobody has, and I think that makes a difference.

DR. MOSCICKI: May I comment on that, as well, because again, these patients that we are talking about were all symptomatic patients, and most, although there is not a lot of good data on natural history, I think the experience of most surgeons -- and I would like to ask Dr. Minas to

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comment -- is that we can expect that the natural history of some patients who have had symptoms as long as this are substantial.

Also, remember that many of these patients have had prior surgery to try and correct this and, in fact, failed, so that depending upon what series you are looking at, the registry or the Swedish series, there is a large number of patients who, in fact, have failed these alternatives, who now appear to be responding to this procedure.

Again, I would come back to the literature issue. If one tries to dig out -- and we tried our best to dig out reasonable comparisons -- but, for example, Jobba's study was mentioned, and again, the patient population in Jobba's study for the largest part were perhaps softballs, if you will, those are patients who had either small lesions or partial thickness lesions, and, yes, they came out well, but when you looked at Jobba's data regarding the patients who, in fact, had full thickness defects, they did terribly out of that study.

So I think again, apples to apples, as close as you can get, this does appear, in fact, to be superior when you take into consideration the age group, the lesion size, duration of symptoms, and I would ask any of our orthopedic

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colleagues here to perhaps comment on their experience and start with Dr. Minas.

DR. MINAS: I would just like to comment on my patient population. I get a skewed viewpoint because I have a referral practice, so I don't treat primary chondral injuries usually, but I do use all these treatment options in my practice clinically.

I use abrasion, I use drilling. I used to use perichondrium until I had a problem with them all turning into bone, and presently I use autologous chondrocytes. In my autologous chondrocyte patient population, the average age is 36 years old. Patients have had on average 2.5 surgeries per knee. They have all failed traditional treatment options of abrasion, drilling, microfracture, or perichondrial grafting.

So they have had the whole regimen of treatment options, and what is the most dramatic thing to me is them coming back to my office and telling me the enormous difference in quality of life they have had within 6 to 12 months after implantation, and that is certainly nothing I could provide to them before with large lesions, on average 6 square centimeters, in the weight-bearing condyles in this patient population, that I could offer them with abrasion or microfracture or drilling.

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Now, on the other hand, on the smaller lesions -- and that is why I mentioned the smaller contained lesions -- that just debriding the loose chondral flaps, I have had other surgeons come to me and say they did a second look six months later, they saw some repair tissue in the defect.

There have been reports of synovial cell migration to help fill those defects, of bone marrow helping to fill those defects, and clearly some of the smaller defects are probably not a problem no matter what method of repair is used for them, and patients have been sent to me with asymptomatic chondral injuries for "cartilage cell implantation." I have asked them, do you hurt? No. Can I see your arthroscopic pictures? They show me the pictures. I see a small divot, and I say, well, if this progresses, I can't treat you now because I could make you worse. So when you come back and you hurt, we will talk about it further, and we will reassess what your knee looks like and see if this lesion has progressed or healed.

So your point about natural history is a very good point. Certainly there are enough advocates of all these different procedures, microfracture, abrasion, that talk about successful results, and the one that I quoted was Dr. Rodrigo, who had presented his results in lesions that are 2 square centimeters or less, 50 percent of those patients

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returning back to sports.

Well, 50 percent of them might have returned back to sports if he didn't do it anyway. In that article that came out last year from Scandinavia by Messner, they talked about lesions 14 years later that were Grade III and Grade IV partial thickness and full thickness lesion that were 1 square centimeter or greater, and that these patients were able to return to sports in 21 out of 28 patients, however, they demonstrated radiographic evidence of joint space narrowing, which is obviously what we want to try and prevent here.

I use all these treatment options, but in my patient practice, patients come, routinely failing. I think that the study that is proposed is very useful because what it will do for us is it will tell us what we want to know. It will tell us what is the success rate of a microfracture, what is the success rate of an abrasion, how many of them fail, and for which size lesions can we successfully try this as a first-arm treatment method, and when should autologous chondrocytes be used as a first-arm treatment method.

In my practice, I believe at this time that for larger lesions that have the weight-bearing surface bottoming out on the tibial plateau, I don't think that

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fibrocartilage is mechanically sound enough that I can use abrasion as a first-line treatment option.

On those large lesions, I would use autologous chondrocytes, I haven't seen one yet, but I would use those for my first-line treatment option, that autologous chondrocytes for me, with the large injuries, are just a dramatic difference in the patient's quality of life.

DR. HANLEY: Thank you.

We have a question from a knee surgeon, Dr. Coutts.

DR. COUTTS: I want to put more of a clinical spin on what we have been listening to this morning and this afternoon. When you are in a room with a patient with the door closed, and it is just you and the patient discussing what you are proposing to help them, we are by law required to inform them, and they are supposed to sign an informed consent.

Oftentimes the difference between a happy and an unhappy patient is the reality with which we can tell them about what they can expect from this procedure.

We have seen the same data presented in different formats, which in final analysis essentially tells us that the outcomes and the results fit along a spectrum that is anywhere from excellent, restitution of normal joint

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function with full return without limitations to something less than that, including some failures.

So there is a degree of variability that is occurring here, and I don't know whether you can say that 80 percent are turning out to be what the patients expect or what you would expect, or whether it is a smaller percentage of that or larger percentage.

I don't want to harp on that, however, because it is clear to me that the treatment is clearly capable of giving a good outcome. What I am more interested in is why does it not give a good outcome.

There is a variability in the quality of the histology that we have seen. Not all of these implantations are producing hyaline-like tissue, whether it is all of the biopsy or part of it, and some of the biopsies are showing distinctly fibrocartilaginous tissue which we know we can produce in another way, much less expensively.

I know that from the company's perspective, you want to put the best possible spin on all this, but still what we really need to do is understand why we have failures, and I would be interested in knowing whether there is any thought been given to why it is that some of these patients don't do well. What are the factors, are they biologic, are they technical, are they mechanical?

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I would be interested in knowing if you have any perspective on this.

DR. McPHERSON: I would make one comment, and that is I don't believe there is a medical procedure that doesn't have variability in terms of the ultimate outcome. I am not aware of anything that has a 100 percent success rate, or it is a very rare situation.

As you have mentioned, there are a number of confounding variables that influence clinical outcomes, everything from the genetic makeup of the individual to his compliance in rehabilitation. There are an infinite number of variables that probably impact the ultimate clinical outcome in any kind of a procedure.

In this particular procedure, I think things like rehabilitation could potentially influence the outcome. How complicated the joint is by ancillary disease that physicians may or may not know about, the nature of the defect, in other words, are there situations where there is a greater degree of injury than one would hope for, and there are cells coming up from the base of the wound that are difficult to control, that are influencing whether or not fibrocartilage is developed or not, there are, as I said, a number of different potential explanations for the variability.

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I do not think variability is unique to this procedure. In the area of wound repair in general, we see a great deal of variability for, again, a variety of reasons. In our cell-based therapies for burn patients, there is variability in terms of graft take. Again, that is a consequence of how well the patients have been debrided, what kind of a dermal matrix is used to engraft the cells on, and so forth.

DR. MOSCICKI: I would like to also comment on that question, because I think it is an interesting and excellent question that you raise. In fact, there are several issues here. One is consistency.

I think it is the nature of human beings and biological responses to be somewhat variable, and I think that will be apparent in any therapy, but actually, I think that what we see is a fairly more consistent result than what we observe in whatever rough comparisons we can make with some of the alternatives that are available. This appears to be more consistent.

I think in terms of consistency, there is another issue, and that is another point of value of the registry data that was asked about earlier, and that, in fact, is that no longer are we talking about one surgeon or two surgeons in one city, but, in fact, now we see that we are

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still getting consistent responses among multiple surgeons in multiple cities across the United States. I think that also is quite variable.

Furthermore, the registry does provide a new standard by which we can begin to answer these questions. We do track the outcomes. We, in fact, have already initiated an analysis on our own to begin to look at those patients in whom the registry has recorded poor outcomes, and begun to go back and look at all of the issues that are already in the registry, with the next step of actually then querying those surgeons about those cases to discover any new issues, but that is the golden opportunity here.

This new standard of rigorous ongoing clinical outcomes information are not available in the past in most other procedures, allows us to do that kind of an analysis.

I think that in terms of many of the failures, we already know that many of these involved very complex revisions. They are not the patients that we think would be the ideal patients for this, for example, in the 2 cm up to 10 or 20 cm² in size.

These are patients who sometimes have kissing lesions. These are patients who have undergone multiple other procedures and therefore have a poor subchondral bone plate already. In some cases, the failures were simply due

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to trauma, where the patient fell. So, we know a few of these factors already -- or didn't follow their rehabilitation protocols the way that they were supposed to.

But I think Dr. Peterson might comment on this, as well, and I know Dr. Mandelbaum is another one of our overseers of the registry and would like to comment.

DR. HANLEY: Thank you.

Dr. Miller, do you have a question?

DR. MILLER: I have several questions I would like to ask. First of all, when I read the proposal, I was surprised that the FDA ever considered not reviewing this kind of thing, proposal or PMA. Now I am glad that they have changed their position and are doing that.

The next thing was when I started to read this, particularly the review of the literature, my impression was I just read a very nice selection of a series of observational studies that laid the groundwork for the need of a well-designed clinical trial.

Then, I went on to continue that reading and I found out that in the U.S., we were considering a registry format for that trial, and in fact it is not a trial, it is best used for follow-up studies.

Secondly, as I read through it, I found out that we were denied the availability of a control group, proper

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control group, and yet as I read these things, it looked to me like there were a variety of opportunities to construct a control group, and I remind this group that a control does not -- the definition of control is not placebo, it is a reasonable alternative or an existing alternative to the proposed treatment, and those alternatives are available here.

I was surprised this afternoon to find out that randomization couldn't be used in this process, in this clinical trial process. I think it could be.

So I am looking at all of these things. I hear people say we are going to accept equivalence here. Well, if you accept equivalence here as your desired goal, you are introducing a really serious problem about sample sizes because, as you recall, all you do is establish the probability that the null isn't true, and you never can, in fact, prove that null hypothesis.

So it just looks to me like the registry is -- you know, you tell me you are going to spend \$6 million, and you are going to have a registry type result. It just doesn't seem rational to me.

So I am glad that the FDA is involved again. I am glad they are asking these questions. I think there is a control group, and I think that randomization could be built

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into this, and you can get the results that you wanted.

MR. SURGENOR: It is difficult to go back and change the history of the evolution of this procedure, and as the FDA has already mentioned, the company made a series of decisions under a certain amount of confusion about where this product would be.

It is more constructive, I think, to talk about where we should go in the future, and I think that is what you are leading to. There are two separate and distinct programs here that we are talking about.

One is the registry program, which is an attempt to collect data from every patient treated, from a product already on the market. So that is one program. It is not a clinical study. We are asking orthopedic surgeons to collect data in their practices from patients that are being treated. We have informed consent for the data to be collected by the company.

There is a separate program, entirely separate program, to perform a post-marketing study. That is one thing. I just want to make sure that those two things are clear. The registry program does have a cost, sir, but it is not \$6 million. It is about \$1,000 per patient that it takes to collect that data.

So when someone asked before, should we collect

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photos or should we collect biopsies, the answer really is no, we are not going to try to collect photos or biopsies from hundreds of sites.

But in a comparative study, which I think is one of the questions that this panel is going to be asked to comment on, we certainly are open to suggestions about how we can improve the quality of that program.

I hope maybe I have clarified those two completely separate initiatives here.

DR. MILLER: I hear the difference that you speak to, but when I see how the difference in interpretation of definitions of function and type of tissue as we saw today in one of these analyses, I argue how dependent is your claim for efficacy on the type of tissue that you are looking at. I don't think that histology is in there.

I don't think that those definitions are clear. I think that there is so much missing in the basic structure of your proposal that -- \$6 million, no matter what you spend it on, that is a misuse of your funds.

DR. MOSCICKI: Can I speak to that \$6 million? That specifically refers to the cost that we project for the comparative trial, not the registry, it is the comparative trial, and in that we are dealing with a homogeneously, prospectively, well-defined group in terms of defect size,

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symptoms, so that both groups will start out looking very much the same using these narrow inclusion/exclusion criteria.

Furthermore, as far as equivalence goes, that trial is not designed to show equivalence, and that is not the issue with that trial. We believe that that is a trial that everybody will want to know in the future as to when orthopedists themselves make up their own minds on using this, and it is designed to show superiority.

The sample size was carefully calculated based on assuming, in fact, that the one group, the Carticel group, in a one-sided test has to prove to be superior to the alternative therapies when you really have this kind of head-to-head analysis.

DR. HANLEY: Thank you. I don't think that the amount of money you plan to spend is under the purview of this committee. I don't think we need to discuss that at all.

DR. MILLER: You are right. I would still like to understand better what your control group is and why there is no randomization process.

MR. SURGENOR: Would you like us to cover that again?

DR. HANLEY: I think it is well laid out in the

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book. If you want to just make a brief comment about that.

MR. SURGENOR: Before Rich does that, let me just make one other brief comment. That study, the post-marketing study that we are talking about, with these various design features, was designed again in the absence of an FDA approval, and obviously, there is negotiation to happen on that, so we are looking for this input.

We will be happy to go back through that again.

DR. MOSCICKI: I think there is a control group. There are two groups in the comparative trial. There is a group of patients, as I mentioned before, that are the same at baseline, and they have to fill a very narrow definition, and that is how we construct the control group here.

One will be essentially randomly assigned simply by the fact of who they present to. It is not a classical randomization scheme, and I understand the scientific attraction of classical randomization, but there clearly is a control group to make a comparison with at the end of the study, which is in five years.

DR. HANLEY: Very good. Dr. Trippel.

DR. TRIPPEL: I would like to come back to this issue of efficacy because it seems to be the major issue that this committee is going to have to deal with. Dr. McPherson made a very important point during his

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presentation, and I will just read from his slide because he said it very well.

"There has never been a double-blind, randomized placebo controlled, multicenter trial performed on any of the therapies currently used to treat full-thickness cartilage injury of the knee."

That is a very harsh, but I think a very accurate indictment of the orthopedic research community. It is reprehensible that we have gone for this long without knowing whether we should use cells or periosteum, whether if we use periosteum we should put it in one way or put it in upsidedown, whether if we are going to use periosteum we need to put a defect in the subchondral bone or not, whether we need to use continuous passive motion in the rehab program or not.

These are all critical issues for which we don't have answers. The solution to that problem, though, is not to come up with yet another one-armed, nonrandomized, noncontrolled report. I am not going to use the word study.

For that reason, what we have heard today is of only minimal, I think, value.

The Swedish study is a very nice attempt at starting to solve that problem, but it doesn't have a control group, and I have personally been very concerned

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over what appears to be a discrepancy between the interpretation of the investigators and an interpretation of an independent medical reviewer.

Similarly, a registry, such as the one that you have put together in this country, is a very nice idea, as will. It, too, is not a study, as you accurately pointed out. It doesn't have any controls, and it makes it a little difficult to understand how to explain the results.

Let me give you an example. One of the statistically significant results that you pointed out was that the cartilage implant improved patella tracking. The problem is that about 75 percent of the patients at the time of their biopsy had an additional procedure besides the biopsy, and about 25 percent of the patients had an additional procedure besides the implant.

So it is a little hard to know which of the interventions was the one that produced the effect. In the case of the patella tracking, I suggest to you that it might well have been not the implant, but the operation on the lateral retinaculum that may have produced that benefit.

The proposal therefore that you have made to do a comparative study is absolutely critical, and I want to compliment you over and over again for that, because that is where we need to go next. I have heard a comment that when

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your product was started, that it was not regulated and therefore this wasn't planned, but anyone who holds your product in high esteem will want to see it get tested in a valid scientific way, so that it has a chance to prove itself.

It deserves a chance to unequivocally demonstrate that it works, and the only way that you are going to do that, whatever the FDA requires or doesn't require, is with good science, and your comparative approach is your opportunity to do that.

Now, I have a couple of questions about that, and one has to do with this issue of control group. The product that you are marketing, if I understand it correctly, is cells. Therefore, if you want to find out if the cells are doing anything, then, the control group has to be whatever you did with the cells, but not with the cells.

In other words, you need to have that periosteal flap in there, you need to have the patients be otherwise similar. Now, you have pointed out -- and I think very cogently -- that there are some potential problems with periosteal flaps.

One is you need to have a source of cells. Can the periosteal flap produce the cells? You have already shown that in your beta galactosidase studies that the cells

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that you put in do work. There are other studies, which you didn't cite, however, that show that if you put in a periosteal flap which has been prelabeled with tritiated thymidine that the cells will fill the gap with tritiated thymidine label, indicating that the periosteum, when used for correction of defects, will, in fact, provide a source of cells. So that isn't the problem.

Another study which you cited was your canine study, and your scientists did a very nice job of designing that study. It was a well-controlled study. It included one group of animals in which there was a periosteal flap alone, and another group of animals in which there was a periosteal flap with the cells.

At six months, if I remember the data correctly -- and please correct me if I am quoting this wrong -- there was a statistically significant difference between those two groups. The cell group was better than the periosteal flap alone group.

However, at one year, they were identical. So that suggests the periosteal flap did just as well as the cells. Maybe, therefore, you don't need the cells. In any event, it becomes an empirical question that needs to be tested.

A third point that was brought up is the

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possibility that the periosteum, because it under normal circumstances can make bone, might make bone in the wrong site. There was a very interesting study that you provided in your packet, I think it is in Appendix E, which shows the results at any extraordinary follow-up, something like 18 years, of a Finnish surgeon's work in which he went back and took biopsies of patients in whom the treatment was just a periosteal flap, and in none of those cases was there any bone. In fact, in some of those cases there was hyaline cartilage in there.

So, the argument against using a periosteal flap alone as a control is not convincing to me, and I still think that it is a reasonable thing to consider as a control, because that way you will have more valid data when you present your results.

I also had a question about this randomization. One thing that worries me is that if you can randomize in an elegant way, why randomize in some convoluted way.

DR. SIEGEL: Just for clarity, they are not proposing randomizing.

DR. MOSCICKI: Not using a classical random element or randomization scheme, but again, I want to reiterate that we are interested in getting good opinions on this. We have opinions from what we thought were good

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orthopedic people, who were well experienced in clinical research, and some of this was based on their opinions. We are certainly open to hearing more about this panel's opinion on both the issues of control group and randomization.

I think we have gone through some of the elements as to how and why we ended up choosing for the current design those elements.

You have raised the issue of the dog study, and I think both Dr. McPherson and Dr. Minas, who was involved in that study, I think would both be appropriate people to comment on that study.

DR. TRIPPEL: The reason for mentioning that study, by the way, was to compliment the design actually and to suggest that because your scientists deemed that to be an appropriate experimental design, good science, that it might be reasonable to apply that same concept to your human studies.

DR. MCPHERSON: One point of clarification, though. In terms of the dog data, you are correct, at six months the sites that were treated with periosteum alone had less fill than the sites that were augmented or supplemented with cells. You also are correct that at 12 months there was no difference between periosteum and periosteum plus

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cells. But the other key point was sites that were completely not treated, no periosteum, no cells, nothing, just a hole, also healed.

So it was a confusing situation in that what appeared to be an effect of spontaneous healing was clouding any result you could see. Beyond that, we also saw osteo degeneration in a number of animals that further complicated the results.

The only point I want to make is that at 12 months, you are right, there was no difference between periosteum and periosteum plus cells, but there is also no difference between defects that weren't treated with anything. So that is just one point.

DR. TRIPPEL: Well, if you want to include an untreated control group in your humans, as well, you could consider that, but, please, at least drill it.

DR. McPHERSON: That sort of speaks to one of the challenges of the situation.

DR. HANLEY: I think the point has been made. In the interest of time, I think we should move along.

DR. SIEGEL: May I make a quick comment because there was something that was stated by a couple of people about the FDA review that I want to clarify, and that is the extent to which it differed from the sponsor's review.

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We reviewed the data by somewhat different standards. We defined a failure, for example, as you heard in one case, of someone who required a definitive second procedure. So we came up with somewhat different classifications in terms of the clinical outcomes.

But as you noted in a 2 by 2 table, the large majority of patients came the same. There were patients moving in both directions. I think that, in fact, in terms of the clinical outcomes, in large part our finding on the Swedish data confirms and certainly is consistent with the finding of the sponsor.

What, of course, I think is highlighted to everybody is the difference in whether or not the histological data correlated with the clinical outcomes. I should note, although this wasn't well highlighted, that the arthroscopic data did correlate with clinical outcomes.

The very few patients who had no defects all had good outcomes. Those who had minor defects tended to have not as good, but centered around good outcomes, and those with major defects had poor outcomes, but on the histological data, there is that difference.

There are a number of reasons why it might have occurred. There are many outcome scales potentially that could have been used, or questionnaire data were used, the

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Britberg scale data were used by the sponsor. We used our chart assessments. There were also differences in the histological outcomes.

I think the bottom line, though, and I think the important thing we all need to keep in mind about that, is that the sponsor's data suggest something that is quite plausible, that the histological data do correlate with outcomes.

Our data suggest that there is not a lot of evidence there suggesting that they correlate with clinical outcomes, however, whichever way you look at it, the data are limited to 22 or 23 biopsies, and I think that nobody would want to make a conclusion based on either analysis. I think it remains very much an open question.

DR. TRIPPEL: Can I just ask one additional, very quick question?

DR. HANLEY: Very quick with a quick answer.

DR. TRIPPEL: Is there any way that a patient without insurance coverage can enter the Carticel group?

MR. SURGENOR: I am sorry, Dr. Trippel, which group, the registry or the study?

DR. TRIPPEL: The comparative study group.

MR. SURGENOR: Not at this time unless we were to develop some new program. All of the patients in the study

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need to be covered, not only for our costs, but also don't forget the costs of the surgeon and the hospital.

DR. TRIPPEL: Okay. That certainly isn't randomized.

MR. SURGENOR: That is a succinct answer.

DR. HANLEY: We have a number of questions that have been addressed to the panel, however, before we move into those, I want to make sure that everyone on the panel has had a chance to address to the sponsor or to the FDA reviewers any pressing questions. Please keep time in mind when you do that.

Dr. Holeman.

DR. HOLEMAN: I think you just spoke to one of the questions that I had. That was the assessibility of this procedure to the vast majority of the population that desire that procedure.

The other thing, when you were making your presentation, one of you said that the physician had to be trained to participate. I would like for you to briefly address to what extent a physician in the population would have to be trained to do this, and if the procedure is so complex, should a physician perform this procedure that is inexperienced, what are the safety issues?

MR. SURGENOR: The first part of the training

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issue is that we do train all surgeons who are provided cells by the service, and that is to ensure that they have access to the information, the information like we have presented today, as well as a chance to use the technique in a bioskill setting, but I think in terms of whether or not surgeons need a certain amount of experience to practice the procedure, perhaps Dr. Mandelbaum or Dr. Moscicki can address that from the registry point of view.

DR. MOSCICKI: I think that it is perhaps not so much a registry point of view. I have been actually pleased that using multiple investigators in the registry, that we do see that some of these physicians who have not done a lot of cases, still, their patients are reporting at least at this early time point of 12 months good results consistent with what we are seeing in many of the more experienced surgeons.

Maybe what you are asking is an issue of medical practice, what is our role, what is society's role, what is the Academy's role.

DR. HANLEY: I don't think we have to spend a lot of time on that. There are many orthopedic surgeons here. Surgeons can be very easily trained to do this satisfactorily.

Dr. Coutts, wouldn't you think so?

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DR. COUTTS: I agree.

DR. HANLEY: It is not complicated.

Dr. Markolf.

DR. MARKOLF: I would like to focus on some of the details of the procedure. How are the cells provided, are they in a syringe with a certain amount of volume? Is the same volume injected into different size defects, because the defects can go from 1.3 all the way up to 14 square centimeters? So, how about the concentration of the cells that you are injecting into the defect?

MR. SURGENOR: Cells are provided in a vial. Each vial has a specified number of cells plus or minus of variability. The surgeons can order multiple vials based on an estimation of the size of the defects, and we provide a mechanism for estimating that.

That system has worked extremely well. We have not had any situations where surgeons have had fewer cells than they require. I think that is a short answer. There is lots more we could discuss in that if we needed to.

DR. MARKOLF: So, basically, you are scaling the number of cells to the size of the defect?

MR. SURGENOR: Yes, we are.

DR. MARKOLF: So you suture this flap with sutures around, and at the last instant you inject these cells in,

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and then you close the last flap. How can that flap be expected to withstand two to three times body weight without squirting the cells out?

DR. MINAS: You are right, they can't is the answer. That is the importance of the physical therapy regimen and training the patient preoperatively what their postoperative care will be.

The postoperative protocol involves crutches and touch weight bearing for six weeks followed by a graduated weight bearing up to three months before they are off of crutches. They then use a cane, and they are usually off a cane by about four to four and a half months.

That goes basically along the repair process whereby we find that usually there is tissue fill after a proliferative phase of healing by six weeks, and this then starts remodeling and starts to integrate by three months. By that time, there is usually satisfactory pain relief when the patient starts to bear weight on it.

Obviously, those are issues that are key for this bioactive incubator is the way I usually tell my patients, I say you have some saran wrap with cells that have to grow underneath it, and basically, until that matures, you are at risk of damaging your graft.

So whether it is done for the trochlea, a

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different protocol was done versus a weight-bearing femoral condyle, a different postoperative protocol was done, and we educate the patients carefully in the hospital before they go home how that is done, and then there is ongoing communication with local therapists as to the postoperative protocol.

DR. MARKOLF: But as you know, just from muscle activity, there is substantial forces across the joint even without weight bearing or partial weight bearing, and it seems that -- we saw in one of the slides this morning, quite dramatic, it looked like a very large portion of the femoral condyle was covered with this very fragile saran wrap, as you point out. It just seems hard for me to believe that those cells are going to stay in the place that you want them to stay for a period of time to accomplish their effect.

DR. MINAS: The suture technique is crucial, and you get a good tight seal before you check it with saline to make sure you don't spill any, and then we seal it with fibrin glue before the cells are injected.

Pretty much from adhesion of cells to the base of the subchondral bone, the adjacent cartilage, and the underside of the periosteum, from the dog model that we did, when we sacrificed a dog acutely at 24 hours after

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implantation, we found the beta-gal labeled cells were well adherent to all the sidewalls.

I think probably a lot of the supernatant or the growth media in which the cells are delivered probably gets absorbed through this semipermeable membrane, and the cells are left behind to proliferate after they have made attachment, and that usually occurs within the first 24 hours.

DR. MARKOLF: But the fibrin glue is now a new element. This is different from the Swedish procedure, is that not correct?

DR. MINAS: No.

DR. MARKOLF: They also use fibrin glue?

DR. MINAS: They also use fibrin glue, yes. It is the identical procedure. The difference, I think is in the cell culturing, differences, which were discussed earlier.

DR. MARKOLF: One final question. I actually reviewed the Britberg rabbit study, and in that he had noted that there did not seem to be adherence between the hyaline-type material and the surrounding cartilage.

Could you comment on that, because I could see a little island of hyaline-like cartilage that is not connected to its neighbors and in the high shear stresses that you can have in the knee, I can see mechanical

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problems.

DR. MINAS: Was that with the carbon fibropad implanted cell group?

DR. MARKOLF: No, actually, that was with the periosteal flap, too. It is right here in front of me.

DR. MINAS: We found that in the dog model, as well, early on. When the sectioning was done at six months, you could see that clearly there was better integration to subchondral bone than to adjacent cartilage, and that is one of the proposed mechanisms of failure as to why the animal model didn't work in the long run, because we couldn't control the animal activity as the animals became more active, and we knew that we didn't have biomechanical integration and firmness as early as six months.

So, when we started proposing mechanisms as to why the animals at 12 and 18 months had evidence of generalized joint disease in all three treatment groups, including the control, as well as spontaneous healing. I mean the animals just became very active once it got comfortable.

DR. MARKOLF: I am just wondering if maybe the human response is the hypertrophy that has been observed around the perimeter of these grafts. Is that maybe evidence of incomplete healing at that joint, or incomplete junction between new cartilage and old?

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DR. MINAS: From my own experience, just when I shave the cartilage, the hypertrophied area down, it felt like when I probe it, you can still see the site of graft to host, but it felt quite firm, it didn't feel like I could separate the interface.

DR. MARKOLF: I would also vote for some type of mechanical probe testing. I think that would be important.

DR. MINAS: There is two mechanical probes that are available, that are just becoming developed. One is the one that Dr. Peterson demonstrated, and there is only one prototype, and he has it, and that is from Finland.

There is another prototype that is available through Professor Guillen in Seville, Spain, which I have been working with, and we don't have that yet. We are hoping to have a prototype. When my first two-year biopsies are coming up, we would like to access them mechanically, as well as histologically and with photography.

There is a third prototype out of MIT, which is a photoelectric prototype, and we are working with them to try to see if can get that to speed. The generalized availability of arthroscopic indentation probes is not that widely available, but we recognize it is very crucial to assessing and determining the repair tissue.

DR. MARKOLF: Thank you.

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DR. NELSON: Just two concerns related to the endpoints of either your registry and the proposed study. One, again, I just want to bring up the issue of the Cincinnati Modified. Without knowing the reliability and the validity of this instrument, you can have any amount of surgeons that want to say that this is a great test, but without having it normed and without having knowledge of the reliability, validity, et cetera, it is to me a relatively useless test. So you may want to consider using or assessing the reliability issue.

The other issue that concerns me is the physician's assessment of the patient at the end. You have 133 physicians maybe doing it now, and they have invested time, money, et cetera. If I did that, I might be a little biased, you know, in terms of aren't you better or don't you feel better.

I would hope that you would consider some kind of activity where a person that is blind to the procedure or blind to the idea that would then not influence the issue, because if I have invested that much time and money into it, I would like to deal with that in a little more objective way.

The last item is have you considered looking at walking patterns. There are several new devices out that

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assess in a very simple way walking patterns and look at stride length, step length, double support time, those kinds of things. I am not talking about a 3-D motion analysis at all, but have you considered looking at the functional issues of walking?

DR. MOSCICKI: I think those are all very good suggestions that we would like to explore further as we gather more data. Again, we chose the Modified Cincinnati based on the best opinions that we could get at the time. We understood Dr. Noyes' development of this instrument was considered by many to provide an instrument that people were familiar with and there was apparently comfort with Dr. Noyes' instrument, and the modifications were made together with Dr. Noyes, so that we solicited his direct opinions in that.

However, I think that particularly as we go forward with the comparative trial, we are interested in thinking about it, and, in fact, in the comparative trial we have carefully discussed adding more max scoring systems, the SF-36, as I mentioned before, is part of that comparative trial.

We will, in fact, use a knee scoring system that was build by the American Academy and that will also supplement the Modified Cincinnati, and if there is a

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consensus that one of these should be the primary efficacy variable, I think we would be very open to those kind of suggestions.

DR. HANLEY: Dr. Friedlaender.

DR. FRIEDLAENDER: First, I would like to congratulate the sponsors in choosing a very important public health issue. I think that the repair and regeneration of cartilage is a huge, huge factor that we have to face, and improvements in this area would be very welcome, and you have obviously spent a great deal of time and effort in providing us with information.

I for one would be upset to interfere with the bringing of a technology to the public that caused some improvement. Obviously, I would be even more concerned in the presence of early enthusiasm in bringing a technology that brought increased risk and hardship to this same huge group of patients.

I need to echo the issue about the efficacy of the cells, because I can see, as a total procedure, the opportunity to prove equivalency. What I am concerned about, though, is why is it working, and this issue about the cells keeps coming to mind in that, first of all, I share Dr. Markolf's concerns about retaining the cells in the defect, and I believe that some of the work that was

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presented showed that tagged cells in very small numbers were found later on.

I also was concerned about the expectation that there would be somewhat of a dose-response curve for the efficacious cells, and that as we saw larger numbers of cells implanted, we saw a lessening of the clinical result, so this dose-response curve was, in fact, inverted, and brings into question at least, because we all believe that this is a cell-based phenomenon, but which are the cells which address this phenomenon.

That brings us back to the issue of the periosteal flap once again, and I think one way or another, whether it is an animal model or some other way, it needs to be addressed before convincing some people, myself included, where the efficacy of this particular approach resides.

I will provide that as a comment because I think in many ways we have gone over that ground.

In the longer term view, I would ask the sponsors if they are concerned about durability and long-term efficacy with a procedure that provides little congruence or fit at the joint surface, either by hypertrophy or by failure of fill, and in the same regard as Dr. Sledge started the discussion, with an architecture, a three-dimensional architecture that is not known for

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durability or the lack of a three-dimensional architecture that, as Dr. Poole would point out, is known for durability.

DR. MOSCICKI: I think that those are all excellent questions, and I think we actually have some good answers. I think Dr. McPherson would like to respond to the issue of dose-response. I know Dr. Minas would like to discuss a little bit about control groups in the human arena. Dr. Trippel said why not do it as you have done it in animals where you can construct that experiment. Humans are different, you have different considerations in human studies. Let me start with Dr. McPherson.

DR. MCPHERSON: I made the comment when I began my talk, I said that all tissue repair is cell mediated, and in this case, we obviously believe that the chondrocytes that are provided following chondrocyte implantation are providing the repair.

In terms of dose, I think you have to understand that the dose that was used was largely empirically arrived at from the Swedish experience or based on the Swedish experience. I mean they did not have a good dose-response kind of an analysis that you would expect for a parenteral, for example, drug that you were using to treat some kind of condition, so the dose is largely empirical.

Now, the question, why does it appear that when

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you put in more cells per unit surface area, for example, the effect seems to be perhaps not quite so good. Until recently, we didn't really have a very good answer to that question, but within the last few weeks we have been doing some experiments -- again, this is in vitro, in cell culture -- looking at the capacity of chondrocyte to redifferentiate as a function of cell density and also look at not only their proliferative capacity, but their ability, as I have said, to make Type II collagen and aggrecan, and so forth.

It turns out there is an inverse correlation between the cells ability to proliferate and their production of hyaline cartilage matrix components as a consequence of cell density.

Again, this is based on RNase protection kinds of analyses, immunohistochemistry and also tritiated thymidine uptake to monitor cell proliferation. The bottom line is that there probably is room to modify the dose based on the clinical data and these new in-vitro data, and perhaps get a more consistent result by more carefully focusing on the dose per unit surface area.

DR. HANLEY: Thank you. Next answer.

DR. MINAS: I was just going to comment on the periosteum as a control group. There are so many variables with periosteum. Dr. Trippel mentioned a study whereby

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tritiated thymidine and periosteum demonstrated that the cells originated from the periosteum.

In a rabbit study, this was done with the cambium layer facing up into the joint, so the cell population was from that layer. That clinical experiment in human population, the results aren't quite as good. I talked about Dr. O'Driscoll's results, 9 out of 15 satisfactory results, 6 out of 15 poor results using that technique.

The technique of putting the cambium layer down in an animal model was done by us, and we couldn't really comment well on that because we, at the 3- and 6-month mark, it was against the empty control. At six weeks it looked like the cells were better than the periosteum alone.

In Dr. Peterson's study that was published last year using rabbit model in the patella with periosteum facing down with cells versus no cells, there was a clear difference, which was highly significant up to one year.

So, in that control group in that animal model, it seemed that the effect of the cells was dramatic. In ours, it appeared that there was an improvement, but we couldn't validate it because we didn't have 3- and 6-month animals with periosteum alone to control against.

In the cell layer upwards with tritiated thymidine, the human experiment for that doesn't seem to be

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working that well, so the question is if we were going to use periosteum as the control, the only other thing that I have in my clinical experience is perichondrium facing up, but then again, here we have a chondrocyte hypertrophy in bone formation, and we already know that periosteum has chondrocyte hypertrophy with Type X collagen expression, so will that turn into bone, as well.

So, what is the direction of the periosteum?

Seeing as we don't have a human control with periosteum down ever published or even a study available in any literature, and an animal model that fails --

DR. HANLEY: We can discuss that in detail during the discussion period if we think it is important. We appreciate your answers. I think we need at some point to get to the questions which the FDA has addressed to the advisory committee.

I would suggest at this time that everybody stand up for two minutes, and we will come back in a few minutes and address the questions.

[Recess.]

Committee Questions

DR. HANLEY: I think we are ready to reconvene and we will now bring the advisory panel meeting back to order.

We have four questions for the panel to discuss

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today. I will read them in order and then we shall return to the first question.

The questions addressed to us are:

1a. Please characterize the expected outcomes for patients with similar cartilage defects and who are managed similarly to those treated in the BLA but without Carticel. In particular, please describe expected short and long term outcomes in patients treated with debridement, lavage, and physical therapy, with or without periosteal flap (or other procedures) in each of the following areas:

- i) functional/symptomatic outcomes;
- ii) arthroscopic findings;
- iii) histological findings.

In the discussion, please comment on the basis on which these determinations are made, for example, through the published literature, personal experience, or other manners. Much of this has already been discussed.

b. In the sponsor's functional analysis, based on retrospective questionnaires, approximately 20 percent of the patients reported less function at the time of the questionnaire than before surgery. The absence of a concurrent, randomized control arm makes it difficult to assess whether or not Carticel could have had a negative impact on these patients. While the Carticel data do not

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suggest any significant systemic toxicities, do these findings raise concerns about local deleterious effects?

2a. Discuss the extent to which, in light of your answer to question 1, these data demonstrate that Carticel has a favorable effect on each of the following outcomes:

i) short or long-term functional/symptomatic outcomes;

ii) arthroscopic findings;

iii) histologic findings.

b. Considering all outcome measures, and again in light of the answer to question 1, has it been demonstrated that the Carticel therapy has a favorable effect on outcome measures and that this effect is reasonably likely to provide clinical benefit in the short or long term? That is the key question we are addressing.

c. Do the arthroscopic and histologic data contribute significantly to your determination?

d. To what extent can it be concluded that the cells contribute to the favorable outcomes beyond the contributions of other treatments, such as a flap?

3. Are there particular patient characteristics, for example, lesion size, lesion location, diagnosis of osteochondritis dissecans, or other diagnostic categories or locations which define a subpopulation, which appear to

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respond differently than others?

4. For the discussed trial, input is sought.

a) What is/are the optimal control treatment(s)?

b) Which patient population(s) should be studied?

c) Which endpoints (functional/symptomatic, structural, and/or histological or others) should be measured, and over what time course?

d) What type of study design is optimal and feasible as recently discussed, randomized, blinded, early versus late treatment, et cetera?

These are the questions that the panel is asked to comment on. One leads into the other, they all are interdependent, and we have discussed aspects of all of these in detail. We will now return to the first question for open discussion.

Again, the question is: characterize the expected outcomes for patients with similar cartilage defects and who are managed similarly to those treated in the BLA but without Carticel. In particular, please describe expected short and long term outcomes in patients treated with debridement, lavage, and physical therapy, with or without periosteal flap with regard to the outcomes discussed, function, arthroscopic, histologic, and what do you base this on.

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The floor is open for discussion, comments. Have we had enough discussion on this already, so that we may summarize?

DR. SLEDGE: I do want to make one comment. I am concerned about the phrase "the Carticel group," since it is not a group in two regards. One is it is not a homogeneous population as we have heard discussed. It is a variety of different lesions. So, it is not a grouping, it is not a homogenous group that can be discussed as a single entity. I think there would be subsets, such as the focal femoral condylar lesion that would be better described as a group.

Secondly, it has not been conclusively demonstrated that the Swedish population were treated the same way. The technical aspects were the same, but there are differences we heard described in the treatment of the cells. So I am not perfectly satisfied that we can extrapolate directly from the Swedish data using cells that they culture and produce and expand, and the current technology. So I think the extrapolation is a little tenuous.

DR. HANLEY: Other comments?

DR. SIEGEL: Let me comment on that comment if you don't mind.

DR. HANLEY: Please go ahead.

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DR. SIEGEL: I would just like to point out that this is a common dilemma in cellular therapy. There is, I think, frequently for the many cellular therapies under development, a constant evolution where people in the laboratory realize technical improvements, you know, they want to get a certain type of serum out, because of risks, they want to put a certain type of growth factor in.

I am not going to offer an answer to that question. What I am going to say is that as we regulate this whole class of therapies, the answer cannot be always to repeat clinical data, since it is just not feasible, so a certain amount of judgment needs to be made about the likelihood that technical improvements in culturing are leading to a variant or improvement of the same product or a different product.

It is a decision we are facing all the time. I would just encourage you to make that consideration on your own basis, but recognizing that facing not complete certainty about what changes will be made, we are often faced with nevertheless having to decide whether we can extrapolate clinical data.

DR. HANLEY: Thank you.

Dr. Coutts.

DR. COUTTS: The question about what is the

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natural history of these lesions I think is unanswerable.

Dr. Minas referred to the types of patients he has seen who have had multiple procedures, and I am not sure that he has seen the natural history of this disease or whether he is treating iatrogenic disease.

The tendency for orthopedic surgeons is to see these lesions and to do something, and then that clouds the picture, so it makes it very difficult to define natural history. The point I am making, I don't think we know natural history.

The other part of the question is do we know how this treatment that, with the information currently available, relates to other treatments that are known. I think the only other treatment which has comparable results to the Carticel method is allografting. That is the only treatment that seems to have any sort of longevity in terms of its outcome. It holds up quite nicely and there is 10-year data on it. Carticel would appear to be equivalent with about a 70 percent good result.

The other methods, despite the deficiencies of the literature in this regard, with lack of controls and comparability to this, generally speaking, give poor results.

DR. HANLEY: I think that is a good summary. I

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think our discussion throughout the afternoon, and with Dr. Coutts' summary, would indicate that from the available evidence, other therapies which have been employed, including debridement, lavage, variations thereof, the results of those treatments are somewhat less than the 70 percent range that have been indicated for the Carticel therapy and for allografting, and this would be true with regard to all types of outcomes, functional, arthroscopic, and probably histologic if we had histology.

DR. FRIEDLAENDER: Excuse me. Are you saying that for long term or short term?

DR. HANLEY: For long term.

DR. FRIEDLAENDER: Okay. But for short term results?

DR. HANLEY: For short term, the discussion today would indicate that most therapies, particularly those involving some type of flushing out of the joint, will have some measurable benefit over the short range.

DR. FRIEDLAENDER: I would agree with that. I just didn't hear that in your response.

DR. HANLEY: I didn't say that.

DR. FRIEDLAENDER: Okay. That is why I didn't hear it.

DR. HANLEY: Thank you for helping me out with

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that.

DR. FRIEDLAENDER: Any time.

DR. HANLEY: The second part of this question relates to some problems associated with the treatment group, the Carticel group. Some patients had problems, there were complications, and these have been addressed in the presentation and the discussion.

The question for the committee is: in the absence of a control arm it is difficult to assess whether or not Carticel could have had a negative impact on these patients. Were there systemic or local toxicities that caused a problem or were the problems related to the performance of the procedure due to the arthrotomy, the section, and that sort of thing?

Comments? Dr. Poole.

DR. POOLE: We never discussed whether or not the actual removal of tissue to isolate chondrocytes from the joint did itself create any pathology, and I think this is something we have to consider as a potential issue.

The other observation, as I said, in looking at two sets of specimens, where we looked at the regenerated tissue and compared it to the normal tissue close by, it was clear that that normal tissue was quite abnormal, and therefore the question is does the chondral defect or does

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the filling of the defect or a combination of both in any way produce pathology in the surround cartilage, and I think we still have to determine that.

DR. SIEGEL: Could I ask a question? Dr. Poole, in your experience, is the occurrence of abnormalities in the tissue surrounding a defect a commonplace occurrence with other approaches?

DR. POOLE: Yes, this is quite common and it really relates I think, as Dr. Markolf has indicated, to the fact that the chondrocytes are incredibly sensitive to the loading, and when you create a defect in the close-by environment, then, the loading changes, and that abnormal loading, because it is not what the cells are used to, can itself create degeneration of that cartilage which was otherwise normal.

So you can have indirect effects on the surrounding tissue by the change in the loading which could be created by either the original defect or the management of the defect. The same could apply to the creation of a defect to provide donor chondrocytes, something which we have never discussed.

DR. HANLEY: Further comments?

DR. SLEDGE: There is a flip side to that, and that may be that there wasn't sufficient resection of the

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abnormal lesion before the procedure. I think it was mentioned by Dr. Minas that when the operation is undertaken, there is a resection back to "normal."

I am not sure how that is determined, but if in the sections you saw there was limited resection or reasons of a conservatism, you would expect to see histologically what you saw. So it may not be cause and effect.

DR. HANLEY: Dr. Kuettner.

DR. KUETTNER: Just in support of what Dr. Poole just said, the latest work of Dr. Eigner from the Max Planck in Germany showed that whenever you have on any side of the cartilage some defect, the rest of the cartilage is responding with an abnormal synthesis of Type II and other matrix components, so the cartilage per se is always responding if there is any damage on one side, the rest of the cartilage will respond with an increased synthesis, kind of a stimulation, so the rest of the cartilage is not dormant.

DR. HANLEY: I would ask the committee if they think there are any systemic effects from this or this just a local phenomenon that we are talking about.

Dr. Coutts.

DR. COUTTS: I think it is fair to say that the effects of this procedure are fairly well localized to the

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joint of concern and that we have not heard anything today which would suggest that there is a systemic effect.

DR. HANLEY: Thank you.

Dr. Trippel.

DR. TRIPPEL: With respect to the local effects, there is I think another possible interpretation of Dr. Poole's findings, and that is that the abnormality is a result of the presence of the defect which causes an abnormal distribution of forces across what once was normal cartilage.

Whether the filling of the defect may have actually decelerated the process is not known. Whether the filling of the defect had no effect on it or whether it accelerated, I think is unknown, so that as far as question (b) is concerned, I think it falls into the same category as question (a), and that is, that we don't have enough data to be able to answer the question intelligently.

DR. HANLEY: I think so, but I think the discussion earlier today, and now, would reflect the fact that we do not believe there are major systemic toxic effects and that local effects are related to how mechanical influences and responses to loading and rough terrain, if you will, occur in situations like this.

Of course, it will occur with the disease process

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itself also because you have a divot, if you will, in the bone.

DR. TRIPPEL: And, of course, there is the hypertrophy that was commented on earlier. Sometimes it is symptomatic. In cases where it is asymptomatic, it may still have an adverse effect on the opposing articular surface over time, but I don't know.

DR. HANLEY: Dr. Poole.

DR. POOLE: Addressing the original defect, again, we don't seem to have any information about because we have not heard about it today or perhaps we have. We don't know how important it is with respect to the management of this defect with this procedure, with respect to the time at which the defect was created.

Do you get a better repair rate if you manage the defect more rapidly than less rapidly, for example, and this is I think something we really have to address - the management of the time-dependent management of that defect, does it affect outcome.

DR. HANLEY: Dr. Coutts.

DR. COUTTS: One final observation. No discussion was given today with regard to morbidity of the donor site.

DR. HANLEY: That was just brought up, and I think that is part of this particular question. The attempted

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answer to this particular question, that we really don't know.

I think to summarize the committee's discussion, in all of the discussion that has gone on today, we really don't know what is happening locally, but they are not major concerns over what is happening systemically with regard to these things. It is not a lack of understanding of this particular thing, is not in and of itself a deterrent to continue to study this process.

Dr. Tomford.

DR. TOMFORD: I would like to just remind the panel that this requires two general anesthesia surgical procedures in contrast to one general anesthesia with scraping out a lesion or something like that.

So in terms of a systemic toxicity, there is the perhaps small, but nonetheless present risk of two general anesthetics instead of one.

DR. HANLEY: Two anesthetics of some sort.

DR. TOMFORD: Anesthetics. Okay.

DR. HANLEY: Noted.

DR. SIEGEL: Before you leave this, two things. One is the issue of the hypertrophy which was seen in about 40 percent of patients, a little over half of those who had arthroscopy. I wonder if there is any comment on that. I

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believe Dr. Minas said some of those patients have catching as a result of the hypertrophy, that is relatively easily managed, but might require another procedure. Is that correct?

DR. HANLEY: Yes, that was my interpretation. He said in his experience it was the graft donor site where he thought the periosteum had ridden up, but there are other reports that we read where, in fact, the cartilage graft, if you will, was hypertrophic and proud, if you will, and was trimmed back.

This seems inherent in at least some percentage of patients that undergo this. I am not sure we have had any evidence to tell us why or how to control this.

Comments?

DR. FRIEDLAENDER: It is clear I think from the past that incongruity, either too much or too little, will affect the long term health of the joint.

DR. LIZAMBRI: I have a comment about the question of whether or not removing the cartilage from the donor site makes a difference. There were approximately four to five patients of the 153 who had biopsy site from the opposite knee, the normal knee. This was often in people who had previous procedures and lacked good donor sites.

There were one or two patients that then somewhat

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subsequently, not immediately, but months to a year or two later developed some problems in that knee, but oftentimes those patients were not completely normal in both knees, but I do recall at least one that had a very normal arthroscopy at the harvesting in the opposite knee, and then subsequently developed problems after that.

DR. HANLEY: Well, there is no doubt that anything you do, anytime you do anything to anybody will have some effect. It is just a matter of how much an effect it has. So I don't think anybody is saying it is not causing any issues. It is just a matter, is it a major, clinically significant item.

Dr. Sledge.

DR. SLEDGE: I think it is fair to say, and should be noted, that there is no articular cartilage that is not weight-bearing or used. If it weren't weight-bearing or used, it wouldn't exist. So I don't think we ought to be too frivolous about the donor site. That is weight-bearing articular cartilage, and I would be willing to sacrifice mine for a procedure that worked, but we shouldn't trivialize the fact of the donor site.

DR. HANLEY: Further comments? To summarize, it is the general opinion of the committee that there are local effects from the performance of the procedure, and there may

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well be alteration in local biomechanical and biochemical issues at the site, but these do not seem to be influencing things outside of the knee, and we don't know the long term effects of that.

Question 2. Discuss the extent to which, in light of your answer to question 1, the data presented demonstrate that Carticel has a favorable effect on each of the following outcomes: short or long-term functional/symptomatic outcomes, arthroscopic findings, and histologic findings.

On (b), we will have a vote of the voting members on the committee. This question is: Considering all outcome measures, and again in light of the answer to question 1, has it been demonstrated that the Carticel therapy has a favorable effect on outcome measures and that this effect is reasonably likely to provide clinical benefit in the short or long term.

Back to (a). Does it have a favorable effect on short or long-term functional, arthroscopic, and histologic findings?

DR. FRIEDLAENDER: Just a point of clarification. When we say "it," do we mean the cells, articular cartilage cells alone or the entire procedure?

DR. HANLEY: The entire procedure.

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DR. FRIEDLAENDER: Not knowing from which element of the procedure the benefit is derived.

DR. HANLEY: The entire procedure which includes the cells, which differentiates it from other similar procedures without cells. Correct?

DR. FRIEDLAENDER: But emphasizing the fact that we do not know from which specific element of this procedure the positive benefit is derived.

DR. SIEGEL: 2(d), when we get to discussing 2(d), we will ask specifically.

DR. FRIEDLAENDER: The sequence in which these will be voted makes it important to clarify this ahead of time.

DR. HANLEY: In my opinion, you are absolutely correct. We don't have enough information to separate and sort this thing out to where the effect comes from. We are talking about the procedure as described which employs cells.

Dr. Rangaswamy.

DR. RANGASWAMY: I have a question. Can we really comment on the long term results given what was presented today? I mean it was brought up even in question 1.

DR. HANLEY: You can comment. Maybe I don't know.

DR. RANGASWAMY: I don't think you should bring it

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up for a vote on that particular issue of long term.

DR. SIEGEL: Let me clarify what we mean by that. Obviously, there is very little 5- or 10-year follow-up, a few patients, but very little here. We were specifically distinguishing, as we did in the MAS cell policy, the 6- and 12-month data from that 18, 24, you know, which you correctly point out that is not exactly long term, but it is a somewhat different body of data since the expectation, as expressed here, has been different for traditional therapies out to two to three years from what one would expect from the same therapies in one year, and much less favorable, but a point well taken, and that the truly long term data we won't have for a number of years.

DR. HANLEY: Dr. Sledge.

DR. SLEDGE: Again, I need clarification. Are we talking about articular chondrocyte transplantation when you say the "Carticel treatment"? If you mean specifically the Carticel treatment, we don't have anything except the registry data, is that correct?

DR. HANLEY: That is correct.

DR. SLEDGE: So if you want to talk about anything longer than six or 12 months, then, you have to go to the Swedish data, which is not the Carticel product.

DR. HANLEY: I think we can use that in our

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discussion. Clarification, Dr. Siegel?

DR. SIEGEL: Well, I think that we would value your judgment on that. We have looked at the Swedish data, our scientists have looked at the validation of cell production, and there were biopsies from a number of patients that were split and cultured in part in the United States and in part in Sweden, and the outcomes were studied and as I understand from our reviewers in terms of cell growth and other outcome measures provided a significant level of assurance to us that the changes made in the procedure were not such that they would invalidate generalization of the clinical data, however, if you are to believe otherwise --

DR. SLEDGE: I am not questioning that. I just want clarification of what we are talking about. I am not questioning it.

DR. SIEGEL: What we are talking about is what has been shown for the Carticel therapy, however, we have been operating under the assumption that the Swedish data are relevant to what we can tell about the Carticel.

DR. SLEDGE: I think if we are going to vote on it, we should stratify and make sure we are voting on either the Carticel or the Swedish data.

DR. HANLEY: Further discussion? Dr. Trippel.

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DR. TRIPPEL: This is another point of clarification. It sounds to me as though we are being asked to vote on something that is different from what is written here, so I would like to request that we either change what we are voting on or change the wording here so that they match.

If we could replace the word "Carticel" with "therapeutic regimen" or "complex of surgical procedures" or something like that, then, we can vote on it, but Carticel is the cells, and we have no controlled studies to look at what the cells are doing or aren't doing, so we really can't vote on what Carticel is doing. We don't have the data.

DR. HANLEY: Clarification, please.

DR. SIEGEL: Yes, that would be helpful. I think as I have indicated in my earlier remarks, we are quite interested independently, in a separate determination, as to whether the overall treatment regimen provided benefit, and as indicated, if that is the case and there is a reasonable likelihood that the cells contributed, we can look to -- you know, we have precedent in looking to additional studies to confirming that, but the independent determination as to whether the combination may provide a benefit and that the cells likely had a contribution, recognizing that there aren't data to make that determination, would be very

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helpful.

DR. HANLEY: So that is what we are going to do. We are going to discuss and vote on the procedure which involves the use of cultured chondrocytes as discussed, not just the cells.

Any further comments on how the procedure employing the cultured chondrocytes influences short or long-term functional, arthroscopic, or histologic findings?

I will summarize our discussion today. We will ask for comments from the panel. It appears from the presentations and from our discussions that there is some short- and medium-term effect that is in excess or better than other treatment regimens employed, such as debridement, lavage, isolated periosteal coverings, and it appears that the patients, from the limited information we have, do better than what we think is the natural history of the disease for patients presenting with symptomatic defects in their articular cartilage in the knee.

So we think they do better functionally and symptomatically in around the 70 percent success range. We can comment on this.

Arthroscopically, we have evidence that suggests, again limited, that the patients that do well have somewhat better looking articular surfaces, not always direct

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correlation, but somewhat better.

The histology is another issue, and from the discussion -- again, I am not trying to inject my personal opinion, but reflect the discussion -- but what I hear about histology is that it is difficult, if not impossible, to correlate the clinical outcome with what the histology looks like, and that more work needs to be done on that.

We may have disparate opinions on this, but the fact remains that it is hard to prove the case that we can make pretty good or hyaline-like cartilage that correlates with the clinical outcome.

My summary statements are now open for correction or discussion.

Dr. Rangaswamy.

DR. RANGASWAMY: When you use the word "better than," it implies that there is a comparison with another method, and it is really not better than. The patients did do well, they did respond, they became asymptomatic, but this really wasn't a trial with any kind of study with controls.

DR. HANLEY: I would alter that to say were improved from their pretreatment state.

DR. FRIEDLAENDER: That is an important clarification and the same one I was going to make. A

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beneficial effect is easier for me to embrace than a comparison, and there was a chart provided to us that showed that the short-term benefits of virtually all of the other alternatives were in the same range.

DR. HANLEY: We are talking about the medium term. We are talking between a year and three years or so, I think, that is the best we can do with the information we have.

DR. FRIEDLAENDER: I was looking at the question and one of the specific portions of the question was short term and the other was long term.

DR. HANLEY: We are not going to address those two issues. I think we will leave it at it appears to provide symptomatic and functional improvement for patients undergoing it in the period beyond a year and up to three years or so, and we are not here to define what short and long term are today.

DR. SIEGEL: Right, but I would like a clarification regarding that distinction between -- I mean obviously, at least in the shorter term, there seems to be consensus with our determination, as well, that a number of procedures that might just involve lavage and debridement also benefit the patient.

I think what you are saying as the sense of the

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committee is that the extent of the benefit extended beyond that is greater than one would expect with alternatives. Recognizing the weakness, and we have discussed this all day, of comparisons, it is not simply enough for us to know that they are better, but that there is reason to believe that they are better than they would have been had they not been --

DR. HANLEY: That is my opinion.

DR. SIEGEL: At least two or three nods.

DR. HANLEY: That is my read on the discussion.

Any comments? Dr. Trippel.

DR. TRIPPEL: If I understood Leela and Gary's points, there really hasn't been the type of study that would enable us to specifically say that it was better. The literature includes, as has been discussed, a wide range of different indications for this, the groups are not necessarily comparable, the treatments are in a wide range of categories, and I think that we would be much safer saying that we weren't certain about a comparison, but that the data is at least perhaps comparable.

Would it be an acceptable compromise to say the same or better than?

DR. RANGASWAMY: I don't think you can say better than unless you have got another comparable group. When you

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say "comparable group," the group should be identical in its demographics and everything. I don't think you have that if you really want to be pure science about this, but I think you can certainly say that the patients were improved. You don't have to make a comparison.

DR. TRIPPEL: How about improved to a similar or greater extent?

DR. FRIEDLAENDER: I don't think that the question asks us to do that. I think in fairness both to the sponsor and our deliberation, it is asking whether there is a favorable response, period.

DR. RANGASWAMY: And there is a favorable response.

DR. SIEGEL: It is asking whether there is a favorable effect on outcome. We are asking are there favorable outcomes that would not be anticipated were the Carticel product not administered.

DR. HANLEY: I think the members of the committee, many members feel that there probably is, is my read, and some do not think they can make that decision because of lack of validated scientific information available. We are talking about clinical opinion versus p value.

I am not sure we are going to be able to resolve that today, but let the record reflect that those are

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concerns of the committee. Some of this will come out in the vote also, because we will see, because that is the real issue.

At this time, I would like to query the voting panel members with regard to their view as registered in a vote on question 2(b).

Considering all outcome measures, and again in light of our answer or discussion concerning question 1, has it been demonstrated that the Carticel therapy procedure -- the whole thing -- has a favorable effect on outcome measures and that this effect is reasonably likely to provide clinical benefit in the short or long term -- and we will eliminate long term since we can't make that decision and short term -- to provide clinical benefit. Is it helpful?

We will now read the voting members.

DR. RANGASWAMY: Can I ask one question? Why is the word "therapy" used?

DR. HANLEY: We changed that.

DR. RANGASWAMY: We aren't using the word "therapy," then, right, we are leaving it out.

DR. SIEGEL: It was used, in fact, for the same reason that you use the word "procedure," that we are not specifically asking whether the product here, but whether

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the therapy including the surgical procedure, the product, postoperative management.

DR. GREENWALD: Would you enumerate, please, 1, 2, 3, 4? What are the outcome measures we are talking about?

DR. SLEDGE: Or would it be simpler just to say outcome?

DR. HANLEY: Outcome. Really, we could pick over this thing all day long. Do you think this help patients? That is the question, it really is.

DR. SIEGEL: Let me clarify how the questions are framed, as well. Under (a) we enumerated so we could get discussion about specific outcomes, but we do need an integrated opinion, did it affect outcome measures that you believe are likely to predict, that are reasonably likely to provide clinical benefit in the short or long term.

I think some outcome measures may be easier or harder to determine for different individuals based on both background and on the nature of the control group. It may be more apparent that it had an effect on histology that you wouldn't have gotten without the therapy. It might be more apparent to some clinically.

But at this point we are asking to integrate as to whether you think it is demonstrated there is an effect, and given that that effect may or may not be based on clinical

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data, we will get to that in (c) and (d), does that effect likely provide clinical benefit.

DR. RANGASWAMY: I think what Dr. Hanley said earlier when he said it provides a favorable response and symptomatic relief, you cannot use outcome measures because we didn't do an outcome study. This was not an outcome study. So there is no way that you can even put that word in, I don't think. It would be totally misleading. So, I think you had better go back to what Dr. Hanley said.

DR. HANLEY: We will go back to "provide a clinical benefit," which means do you think it helps patients.

I will read now the voting members, the appointed voting members, and ask you to state your name, please, or I will read your name and give me a yes or a no to the question.

Dr. Keith Markolf.

DR. MARKOLF: This is not voting for the BLA, this is just this question?

DR. HANLEY: Correct.

DR. MARKOLF: Yes.

DR. HANLEY: Leela Rangaswamy.

DR. RANGASWAMY: Yes, knowing the changes we made in the wording.

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DR. HANLEY: Daniel Clauw.

DR. CLAUW: Yes.

DR. HANLEY: Gary Friedlaender.

DR. FRIEDLAENDER: Yes.

DR. HANLEY: A. Seth Greenwald.

DR. GREENWALD: Yes.

DR. HANLEY: Klaus Kuettner.

DR. FREAS: His vote, Mr. Chairman, was yes, and he had to leave to catch an airplane about two minutes ago.

DR. SIEGEL: The record probably should show that he voted on the question as originally worded, not as reworded.

DR. FRIEDLAENDER: He was here for the full discussion. He just left two minutes ago. He voted on the way the question was modified, yes.

DR. HANLEY: Thank you for that clarification.
Clinton Miller.

DR. MILLER: I am abstaining. I see this is a clinical decision, not a scientific one.

DR. HANLEY: Roger Nelson.

DR. NELSON: Yes.

DR. HANLEY: Anthony Poole?

DR. POOLE: Yes.

DR. HANLEY: Clement Sledge.

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DR. SLEDGE: Yes.

DR. HANLEY: William Tomford.

DR. TOMFORD: Yes.

DR. HANLEY: Stephen Trippel.

DR. TRIPPEL: Yes.

DR. HANLEY: Thank you.

DR. FREAS: Mr. Chairman, that is 11 people voting yes, and one individual abstaining.

DR. HANLEY: Thank you. On our committee the chairman votes in the case of a tie. I believe this is our committee meeting, correct?

If your answer to 2(b) is yes, please discuss the following -- the answer was yes -- do the arthroscopic and histologic data contribute significantly to your determination? Further discussion? Dr. Coutts.

DR. COUTTS: I was just sitting here thinking that maybe you might want to divide that question and ask about the arthroscopic and then the histologic separately.

DR. HANLEY: That is what I think. Let's start with arthroscopy. We had some of that discussion right before our vote. Arthroscopy, do you think the reports we have received of the arthroscopic findings post-treatment correlate with the results and indicate that it is a beneficial procedure?

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Dr. Trippel.

DR. TRIPPEL: I don't believe that the arthroscopic findings were quantitated, and the number of individuals in whom arthroscopic findings were reported as a percentage of the total of the patients who were analyzed is low.

DR. HANLEY: I think that is a fair assessment. The good ones they showed us looked good, and we don't know about the other ones.

DR. SIEGEL: I think arthroscopy was about 80 or 90 percent.

DR. COUTTS: No, they reported on 82 patients that had had arthroscopy.

DR. SIEGEL: I am sorry, 86 patients.

DR. COUTTS: Yes, and there was a reasonably good correlation between the arthroscopic description, and they were categorized in a semi-quantitative fashion, and there was seeming correlation without benefit of a regression analysis. There appeared to be a correlation between the arthroscopic finding and the quality of the outcome.

DR. HANLEY: Dr. Friedlaender.

DR. FRIEDLAENDER: We are talking about a clinical benefit for the short term only?

DR. HANLEY: For the non-long term, yes.

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DR. COUTTS: And this is Swedish data.

DR. FRIEDLAENDER: I don't have any problem.

There isn't a correlation -- there may be, but I don't need that, no. I didn't see that.

DR. HANLEY: Correct.

DR. SIEGEL: Let me point out because I think this was a little unclear. Around the fifth or sixth page of your slides from the FDA are the data about that. Of those who had microscopic integrity at a high level without minor defects, there were only four, and all four had resumed normal activity.

Of those with minor defects, 12 had resumed all activities, 22 had some improvement, 11 had no improvement. Of those with major defects, only 1 resumed all activities, 7 had some improvement, and 11 had no improvement. So I think that is what you were referring to in the data, suggesting a rather strong type of correlation between those outcomes.

DR. HANLEY: Let me attempt to summarize this.

We have been shown some information that arthroscopy may correlate to some degree with clinical outcome, but we have insufficient evidence to say that it absolutely does.

Histology, we do not have evidence that suggests

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that there is a correlation between the histologic findings and the outcome.

DR. COUTTS: I think it is fair to say that it is confusing. There is data, it is very confusing.

DR. HANLEY: I think it would be very important to say I am not saying that it does not correlate, but we have no distinct evidence that it has a direct correlation.

DR. SIEGEL: Let me make sure that we are clear about what the question is because this question is important in terms of the various regulatory strategies I discussed up-front.

We are not asking whether these data have been validated as surrogates, whether you can determine that something works from histology or arthroscopy. We are asking, in your integrated decision that there is reasonably likely to be clinical benefit, is that based entirely on the clinical outcomes or do the clinical outcomes per se support that or is there a significant contribution from the results observed in arthroscopy and in histological data that lead to that conclusion.

So it is a somewhat different question from the way you are phrasing it. I want to make sure we have it answered in the right way, so that I know what to do with the answer.

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DR. HANLEY: Leela Rangaswamy.

DR. RANGASWAMY: This is really a clinical decision? You know, it goes back to the old thing of surgeon saying you have a gut feeling this is going to work, but this does seem to work clinically, but I don't think any of the other data can be used to substantiate what we have said. I mean it is there, it is interesting data, one can look at it, but I am not sure it adds significantly even if you change the wording.

I think it doesn't really contribute to the determination we made, because that was based really on a clinical decisionmaking, not on science here.

DR. HANLEY: I think we have a dilemma here between scientific methodology and clinical practice of medicine. I think scientifically, we are having a difficult time validating this. I think the orthopedic surgeons may use a little bit of everything to come into their decision.

Dr. Poole.

DR. POOLE: This is a problem because we just don't have enough data to really say scientifically whether or not we definitely feel this process is working, but based upon the data that we have, we clearly can say that there are successes and failures. We cannot generalize and say that there is always success.

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We all know there are successes and failures. We have to understand why there is a difference. But when we look at the data, we realize at least in the short term there are clearly benefits. That is why I said yes, but in the long term, if we have histology like that, we are going to be concerned, at least I will be, about long-term outcome, because of inability to sustain a proper loading of the cartilage.

DR. SIEGEL: Are you saying your yes was based in part on the histological assessment?

DR. POOLE: In part, because there was some successes, not perfect as I said in my report. One has to recognize that. This is the very first time data of this kind has been generated, and it is far, far from perfect, but it is very encouraging. That is why I was positive in my final statement in my report.

DR. HANLEY: Dr. Coutts.

DR. COUTTS: I would like the record to show that there are different kinds of science. There is the basic science we have been talking about, and there is clinical science, and we are going to be more and more dependent upon and will be making decisions in the future based on clinical science, and we have had some clinical science presented to us here today.

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I am not commenting on the quality of the science, just that we have had some clinical science, and it is on that basis that we are also making some decisions.

DR. HANLEY: Thank you. I think that summarizes how we got at our answer on those issues.

The next question we have visited and revisited, and let's go again. To what extent can it be concluded that the cells contribute to the favorable outcomes beyond the contributions of other treatments, including the periosteal flap?

Dr. Friedlaender.

DR. FRIEDLAENDER: I have yet to be convinced that the cells are the sole source or the primary source of the improvements and benefits that we have been talking about. It would not surprise me if they were, I just haven't seen the evidence.

DR. HANLEY: Dr. Poole.

DR. POOLE: For this reason we have to have a proper control study.

DR. HANLEY: I think that reflects what the discussion has revealed before, and we need some more work on that. We don't know.

Question No. 3. Are there particular patient characteristics which define a subpopulation, which appear

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to respond differently from others?

Who is the best candidate? We had discussion about the femoral condyle lesion, the tibial lesion, the patella lesion, the osteochondritis dissecans lesion. The information presented clearly favors the femoral condyle lesion as the best in their results although they have new data, they say, that says that the patella is doing better than it did before.

Comments?

DR. SLEDGE: We didn't talk about the OCD lesion, the osteochondritis dissecans, because I didn't see stratification by age, and I think it is fairly well known that that lesion before the growth plate is closed, has a very favorable natural history, so I would say that that is a group that probably should be excluded from study.

There is another worrisome thing we didn't comment on. In the Swedish data, it looked to me in sort of a rough summary that patients who had a femoral condylar defect plus and ACL-deficient knee had better improvement with a combined autologous chondrocyte transplantation and repair of the anterior cruciate ligament than those with femoral condylar defects alone.

Then, we saw data that said at initial arthroscopy, I think it was 2 or 3 percent had focal

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cartilage defects at the time they were first arthroscoped with their ACL defect. Later, when they came to the surgery, it was 20 percent. It suggests that that is a different lesion, it is not a traumatic lesion, perhaps it is related to the deficiency of ligamentous instability.

So I think that group would be worrisome and would contaminate with another variable the purity of a clinical study.

DR. HANLEY: I would agree that fixing their anterior cruciate ligament alone may have provided the same degree of improvement, we don't know.

Dr. Miller.

DR. MILLER: I was going to say it seems to me like this is one of those questions where we don't have the data. In saying that, for example, when we talk about the patient's characteristics, we should include patient behavior, and we heard very late in the conversation about the influence of post-operational behavior of the patient and how that influences the effectiveness of the cells you put in there.

So it seems to me like that has to be taken into consideration.

DR. HANLEY: I think that was made in the presentation that you need a motivated, cooperative patient

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who can perform the rehabilitation program. I don't see much debate here about that.

Dr. Trippel.

DR. TRIPPEL: I would just like to support what Dr. Sledge said, and that is that, in fact, we really don't need to worry about whether the person did or didn't have the ACL out at the time because we are talking about the entire therapeutic program, and that includes ACL reconstruction for the patients who needed it. It doesn't include it for those who didn't need it. So we have got all comers covered.

DR. HANLEY: So you are saying that we cannot define a particular patient subpopulation which is different or we can define every population there is?

DR. TRIPPEL: What I am saying is it doesn't seem to matter whether the ACL is in or out initially if reconstructing it as a part of the therapy corrects the problem for you.

DR. HANLEY: I agree.

Dr. Poole.

DR. POOLE: Actually, I think the OCD group is extremely interesting and important, and Dr. Lizambri drew our attention to it. One of the very interesting features of OCD is that there is clear evidence for vascular invasion

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into the cartilage, and this could promote the healing of the defect.

In fact, this looked like one of the best groups based upon the limited data, and that could well be because of the nature of the disease process which features an angiogenic process of cartilage invasion, which we don't see in any of the other groups ordinarily except in rheumatoid arthritis.

DR. HANLEY: My take on this is that we can't define too many subpopulations.

DR. SIEGEL: There is not a lot of patients, but I would like a clarification from Dr. Sledge, your comment about excluding OCD patients from evaluation. That was specifically those who were young enough that their growth plate hadn't closed. Is that correct?

DR. SLEDGE: Yes, it is a different pathophysiological process.

DR. SIEGEL: Are there any comments on how, in adults, how the likelihood of repair with, let's say, lavage, treatment alternative procedures in OCD compares to the likelihood or expectations in, let's say, traumatic injury in athletes?

DR. SLEDGE: I tried to do a literature survey on that before I came, and I could only find two papers that

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addressed the natural history of OCD in adults untreated. Both suggested it leads to progressive osteoarthritis untreated in adults.

DR. RANGASWAMY: When you want to define a subpopulation, are we defining it because we want to place a restriction on it?

DR. SIEGEL: Right now we are just looking for expertise, not specifically looking for that. If there were a general feeling that some subpopulation was clearly so different that you felt that way, we would want to hear that.

DR. HANLEY: I don't hear that in the discussion other than my comments that possibly the undersurface of the patella doesn't do as well from the information presented.

DR. GREENWALD: There is one subpopulation, and that would be open growth plate patients, and you would really want to exclude those from this whole discussion because the mechanism of nutrition and survival is entirely different.

DR. HANLEY: Let's move forward here to another large issue concerning further studies which may be undertaken.

If a study was to be undertaken, let us discuss issues concerning the type of study and controls, that sort

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of thing. What is the optimal control treatment? Dr. Friedlaender.

DR. FRIEDLAENDER: We have been talking about isolating the contribution of the transferred cells. One way to do that would be to destroy the viable cells in the periosteum, keep it, and there are a variety of techniques to do that. You would have a periosteal or periosteum substructure. The barrier should be identical, but you would have no cells to contribute to the repair.

DR. HANLEY: In that way you would overcome the issue with regard to putting a periosteal flap over with no cells?

DR. FRIEDLAENDER: You kill the cells in the periosteum and you retain the fibrous nature of that structure, and away you go.

DR. HANLEY: That is an alternative to just putting a periosteal -- another, not an alternative -- another control group aside from just putting a periosteal flap and no cells, correct?

DR. FRIEDLAENDER: Correct.

DR. HANLEY: Dr. Trippel.

DR. TRIPPEL: I would be a little bit concerned about that patient population from an ethical standpoint. I would be uncomfortable putting dead periosteum in there and

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no cells.

DR. FRIEDLAENDER: We do that all the time. That doesn't concern me at all.

DR. TRIPPEL: Where are you going to get your repair cells from?

DR. FRIEDLAENDER: The cartilage. Transfer the chondrocytes just like they are right now, but render acellular the periosteum, and thereby you have eliminated it as a source of cellular repair.

DR. TRIPPEL: So you are not proposing to use a periosteum alone.

DR. FRIEDLAENDER: No. I was responding to, in fact, this is only one alternative, but it is the one that would convince me that the benefit was being derived from the transplanted cells.

DR. HANLEY: That gets around the issues that were brought up before, we don't think we can do this with the flap alone, we need the cells from the sponsor.

Dr. Trippel.

DR. TRIPPEL: I have another ethical concern with that design, and that is --

DR. FRIEDLAENDER: I disagree with that, too.

DR. TRIPPEL: -- it mandates that the patient receive two surgical procedures. It doesn't give them the

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opportunity to see if they can have a successful result with only one surgical procedure, which might be possible if you have periosteum alone and in which case the cells come from a periosteum.

DR. HANLEY: That is another potential control group. You don't always have to have just one control group.

DR. FRIEDLAENDER: You are making it too complicated. First of all, it is already a two-procedure effort. Secondly, it is possible to retrieve a small amount of fibrous tissue in a relatively confined, controlled, small type of procedure. Thirdly, you can get it in an allogeneic sense if you really wanted to, I suppose. I think there are ways to overcome that.

DR. SIEGEL: We will certainly have more detailed discussions in the ensuing days and weeks. There are a couple of concerns. We may not be able to hammer out all the details. I think I am hearing a clear message that there is a concern about periosteal flap.

I know one of the issues that has been raised is not just a cellular contribution, but that it may be making important growth factors, in which case that design per se may not answer the question as to whether the cells contribute because a lack of activity might be because of

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the lack of periosteal cytokines.

I guess I would want to think about whether doing such a procedure, even if informative, but without any possibility of benefit to the patient, if that is a reasonable trial. But I just toss that out there now, you know, I think these are issues that are going to need some more in-depth discussion.

But one thing in terms of the control group that we want a very clear picture of is that the proposed control group currently involves abrasion, involves abrasion or microfracture to get basically into the bone.

As noted, it is proposed that it be designed as a superiority trial, and I think a question we have had some discussion on, but some additional would be useful, is, is that a useful control or is it more critical to have a control that will really tell us, compare these cells to something more similar and determine whether the cells per se as opposed to the flap and other parts of the process contribute to the efficacy.

DR. HANLEY: Dr. Poole.

DR. POOLE: I think we have got to come back to Carticel. We are talking about cells, and if we are going to control for the cells and see if the cells are really important, we should keep the flap there and leave the cells

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out. I think that is the only way we can control for this.

DR. HANLEY: Dr. Sledge.

DR. SLEDGE: I would like to mention one very simple control, and that is the patient him or herself. If you adopt valid outcome measures, such as SF-36 or Womack, I think it would be very interesting and very powerful to see the patient himself or herself plotted against time before the procedure, and if you see a steady state with a low score on SF-36, Womack, or some other validated instrument, and then see a sustained improvement afterwards, then the patient is their own control, and I think it is very powerful information, very simple, and very ethical, Dr. Trippel.

DR. SIEGEL: The majority of patients in both continents had prior procedures, and we have had interest in looking to -- obviously, they were selected for having failed or they wouldn't even be here -- but we have been interested in looking at those at the time of failure and comparing it to Carticel. The problem is going retrospectively, it is hard to make too much sense on the outcomes on the earlier procedure. There are some data, but obviously, prospectively, one could do that a lot better.

DR. HANLEY: Let's go back to this question we have been going at all day long. Do members of the panel

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think it is appropriate or necessary to have a periosteal controlled group without cells?

DR. GREENWALD: Yes, I do. I do because, quite frankly, the mechanical environment associated with the internal tensile stresses within the remaining cartilage, the underlying compressive loads that act across the periosteal flap, I would find it very difficult to accept that these cells are not being distributed around the joint space with some proper retention.

You might be just ending up with a diminishment of cells at the very beginning of the process. So why not go the whole way and define the control rigorously as saying a periosteal flap with no cells.

DR. HANLEY: Dr. Clauw.

DR. CLAUW: I am a non-surgeon, but I just asked my friend here, and he said that there wouldn't be any problem in doing this. What I am wondering is why you can't use a periosteal flap and do the drilling and abrasion that they had been talking about doing, and have that be one control group, and then the other control group is the group that gets the Carticel, but we would be sort of isolating, we would only be adding cells in one of these two groups.

DR. RANGASWAMY: If you want to test to prove or to disprove that the cells are responsible for the change,

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then, it is probably better and probably more ethical from the point of view if you have patients coming in to basically offer them the same procedure essentially, and put the cells in both patients, and change one other variable. That would be the most reasonable way to do it.

DR. CLAUW: I think what we are struggling with here is the difference between science and ethics, and what I am saying is that ethically, everyone would agree that if you did drilling and abrasion, and then did a flap, there would likely be some benefit from that, and then the other group was a group that got the flap plus the cells, we would have a good idea if that group was superior that Carticel was doing something. I completely understand, but we can go back and forth forever.

DR. SIEGEL: If five years from now those two groups look not much different, then, what do we know?

DR. RANGASWAMY: That it is equally good, that's all.

DR. SIEGEL: Pardon?

DR. RANGASWAMY: That it is just equally good. It is not any better or any worse, it is just the same.

DR. TRIPPEL: And that you have spared the patient a second operation. I would just like to support what Dr. Clauw said. I think that is a very elegant way of designing

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a nicely controlled experiment, because there what is being tested is a constant periosteum that is stable as a control, as a controlled variable, and the difference is now whether the autologously transplanted cells are better than the patient's own marrow-derived cells that come up and fill the defect from below. That is, in my opinion, a very nice design.

DR. RANGASWAMY: But it still doesn't answer the question of whether the periosteum had anything to do with it, so you are back to square one again.

DR. TRIPPEL: It does test whether the cells that have been implanted have anything to do with it.

DR. HANLEY: I think we have beat this around enough.

DR. SIEGEL: We may have to come back to this committee because, as Dr. Rangaswamy said, if the goal is to determine at the end that they are equally effective, one needs to know how close they need to be, because one needs to know how effective the comparator is, and it would be interesting to hear your opinion on the effectiveness of abrasion with periosteum. But we will have to save that for another day, I think.

DR. HANLEY: I do want to address one issue on the control group, though, and that is the proposed control

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group, which is microfracture or abrasion.

DR. TOMFORD: Dr. Hanley, I don't want to muddy the waters, but really the cells come in something that may have some growth factors in it, so to really do this, what you have to do is have the sponsor provide the vial without the cells with whatever else the cells are in, put the periosteum on, and then put that under. That is the real control.

DR. HANLEY: Good point.

Now, let's go back to that question, would it be satisfactory to have the control as proposed.

DR. FRIEDLAENDER: I don't think it will answer the question as to whether the cultured articular cells have contributed or not to the benefit.

DR. HANLEY: I think that answers the question. So we do not think that is an optimal control, and we do not think that that can answer the question of what benefit the cells --

DR. SIEGEL: But if you added the flap to that, that would answer the question or come closer? I think you said it would, Dr. Trippel.

DR. FRIEDLAENDER: Then, in my mind, if they were equivalent, it would suggest that the cells were of no value. That would be the problem.

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DR. HANLEY: I think that is about as far as we can get that one.

We have discussed (b) before. What patient population(s) should be studied? The sponsor has proposed this application for femoral defects. I don't think we are looking at other applications, although it could be used for that, but femoral defects, should there be restrictions on the populations?

DR. GREENWALD: Are there going to be virgin defects or are they going to be defects that have resisted additional forms of therapy?

DR. FRIEDLAENDER: I think you need two comparable groups to be compared.

DR. RANGASWAMY: Are you going to offer this, then, as -- I guess the question is, is it going to be offered as a first line of treatment or is it going to be like we have tried everything else and nothing works, and therefore, we will try this?

DR. HANLEY: You don't have to be exclusive in that.

DR. RANGASWAMY: You can have two groups of patients, right.

DR. HANLEY: You can have two groups. You can have primary surgeries for defects of X size to X size, and

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previously treated populations femoral defects of X size to X size, and compare those.

DR. RANGASWAMY: But if you do the control study, then the control population, whatever you do for them, whether it is the debridement or whatever it is that you do, must be identical to this group. If you have two groups here, one with the virgin knee and one that has been operated on, they must have the same or --

DR. HANLEY: Those would be subgroups, correct.

Any further discussion? I don't think we can pre-select out any group.

Which endpoints should be measured? I think we all think that they all should be measured, but what is reasonable? If it is a post-approval study, functional, symptomatic outcomes, of course, I think there is universal agreement on that.

Structural and/or histological. I presume structural means MRI or arthroscopy, looking at it, or indentation, Dr. Markolf, which is excellent if we can get the tools from wherever they are coming from.

And/or histological. I think histology is the discussion. Should a post-approval trial involve reoperations, take specimens for analysis under the microscope.

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Dr. Poole.

DR. POOLE: We have to address integration with the existing cartilage. This is absolutely essential as I said earlier.

DR. HANLEY: We are talking theoretically about a post-approval study.

DR. RANGASWAMY: Can you, I guess in all good faith, an asymptomatic patient two years later comes down the road, and you say, gee, I would like to look in your knee and take a piece out? I think it is very difficult to offer that kind of thing to somebody.

I think the patient has symptoms and they come back in, that is a whole different thing, because then you have a different group of patients. I am not sure that ethically you would feel -- if it was my knee, I certainly don't want somebody to look at it. I would prefer them to have some other method, so they could estimate whether the cartilage is intact or not.

DR. HANLEY: Dr. Poole.

DR. POOLE: It might be doable with MRI if people set up experiments reproducing this defect, for example, in a cadaver, and seeing if they can see the defect in the cadaver, and then, say, put the plug back in and see if you can see the presence of a junction because there is no

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integration. So the potential for looking at it with MRI is there, and I would strongly encourage that to be pursued.

DR. HANLEY: I would agree. I think if you are designing a post-approval trial, you can't subject patients to that, so that non-invasive structural measures, such as MRI, are the appropriate things to do.

Any disagreement with this?

Big question. (d) What type of study design, randomized, blinded, early versus late treatment is optimal and feasible?

Dr. Rangaswamy.

DR. RANGASWAMY: In today's climate with all the constraints I guess that we have on just the practice of medicine and everything else, can you really do a true, pure randomized study? The patient has to give you informed consent, you have to discuss the pros and cons of all the procedures and all the various options, so therefore, how does it become randomized? The patient preselects in a sense and decides if they are going to see a particular doctor. I am not sure how you could do a randomized, a pure randomized study. You can do a control study. I am not sure that it can be blinded in this instance because this is again involving two surgical procedures on a patient, and you have to explain all this to the patient.

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So I would like some clarifications as to how does one go about doing that.

DR. SIEGEL: There have been a number of designs proposed for randomization. What was proposed from the company is not a randomized trial. It is one where the treatment is determined by the patient's selection of physician.

One can do randomization to treatments, the treatments that are available at the same center. As long as the patient consents, there is not any restraints to that from an ethical point of view. If the two treatments are considered appropriate for study and they are both available to the patient, that can be done.

The Agency has had some concern about the impact of a lack of randomization on interpretability of results out of such a trial, although there has been some expression of concern about -- that you raise -- about the ability to randomize. So we are particularly interested in -- I don't think there is anything intrinsic to today's environment, in either pre- or post-marketing that makes randomization impossible. We see it all the time. If there is something special about this disease or therapy that you think is problematic, I would like to know.

Blinding. There has been a lot of discussion. We

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will, depending on the control or whatever, I assume ask for as much blinding as possible. That is always good. There might be blinded evaluators if there can't be blinded treaters. There was one suggestion that I think deserves pursuit, of a cell-free population to inject that might allow even higher levels of blinding.

I think that is something that depends on the control, it will depend on discussions, but we are particularly concerned about the implications of patients using different physicians and which different types of patients go, and what this committee thinks about randomization in such a setting.

DR. RANGASWAMY: I still don't know how you would randomize it, how you would randomize this particular procedure. I am not sure.

DR. SIEGEL: Based on the fact that you are not likely to have physicians equally trained in both, if a patient would show up at the medical center and would be offered a trial in which if he were randomized, he would have physician A do treatment A, or physician B do treatment B. If, however, the control, as many of you have suggested, is a flap with or without injection of cells, it probably could be the same physician. If the control is something, as some of you have suggested, different, such as abrasion

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or microfracture, it might be preferable to have it differently, but as long as the patient consented, there is certainly nothing that has been said by this committee that would suggest that any of those options would be considered ethically unacceptable or medically inappropriate, and so a patient could be randomized using traditional random number generators, and would have the appropriate procedure by the appropriate provider.

DR. HANLEY: That is one way to do it. It could be blinded also if you elected one way that has been selected, where you do the flap and inject the liquid without the cells, the nonexperienced probably wouldn't know the difference, just to get the juice back and put it under, and sew it up, and open it.

This is again post-approval, so that it brings in all kinds of other issues that we are talking about, and easy to say, but more difficult to do in the post-approval. It is easy for a doctor to present to a patient a study where he really has no intrinsic bias, where he says I really don't know which one is better, we have designed the study where everything is the same except for one little thing, and we are going to pull a number out of a random table and do it. But it is very difficult to randomize if a doctor has a preconceived bias or belief, which we already

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have with this particular problem even before there was any scientific evidence.

DR. SIEGEL: But there are other therapies out there, and I mean in oncology, approved drugs, people are randomized all the time to different regimens of approved drugs.

DR. RANGASWAMY: Drugs are easy to do. This is not a drug.

DR. HANLEY: I think we have brought up the issues to discuss here, that everybody believes randomization is better because it is more scientifically valid. Everybody believes that blinding is better because it is more scientifically valid. But we have to work within the constraints of the situation at hand and design the best study possible that will permit patients to be treated ethically and still have buy-in from participants of the study, i.e., the doctors.

Dr. Miller.

DR. MILLER: As we come to closure here, I would like to see this design make some attempt to examine those people that are lost. It appears that you have a lost to follow-up of somewhere around 30 percent dropout rate, and I would like to know a little bit more about them.

DR. HANLEY: We can make a recommendation that an

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attempt be made to continue to follow these patients that are in the registry here and go out and fill in the numbers as best as possible. I would assume the sponsor is attempting to do that, but we could make the recommendation that more information is better, and there are ways to do that rather than the routine that can optimize it.

Dr. Trippel.

DR. TRIPPEL: Is there any way of making this recommendation a little bit stronger? This problem of articular cartilage repair has been plaguing orthopedics for centuries, and this is almost a unique opportunity to solve the problem once and for all. The last thing we need or that anybody needs, the company, the patient, is a study that will be subject to criticism. It must not have an Achilles' heel.

So maximizing elegance and rigorous science should be the way to go with this. Anything else will only be a waste of everybody's time and resources.

DR. SIEGEL: I would like to say that the comments of this committee on study design are likely to be critical to the doability of a study. If this committee says it is appropriate and important to have randomization, I think that makes it that much more likely that such a study will happen.

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I am not sure if I understand from your comment, Dr. Hanley, in saying randomization is desirable if achievable, are you comfortable that if not, that patient selection of which treatment they get, or which physician and thereby which treatment, is an adequate way to do a study?

DR. HANLEY: That will be a suboptimal study. My comment is that it could be difficult to do. I am always in favor of the randomized thing, and I would come down in favor of that in this and in every other thing, but I have some worries that it may not be doable.

DR. RANGASWAMY: I have one comment. I assume that all the people who will participate in this trial will be IRB approval before they do this, because if they then want to publish it, that is one of the things that most publishers now look at.

DR. HANLEY: Well, you are just bringing up that other issue. Post-approval studies are a completely different bird than pre-approval studies, which are investigational studies that are mandated to have IRB approval, but as part of this, we are trying to, in a special circumstance, reconstruct some appropriate information, and we would advise that it be subject to IRB approval. Of course, it has to be because once you gather

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data on individuals, you are obligated to do that. We hope that everyone does that.

I think we have addressed the questions as best we can. I think we had a unique and somewhat difficult situation today to discuss. We would thank the sponsors for their excellent presentation and their patience today. Thank you particularly for the trials and tribulations of going through the answer period.

I would like to thank the FDA people who participated in the review and presentation, and assisted us in this discussion, and I would especially like to thank all of our old and new members of this combined advisory panel.

For those of you who are working tomorrow, we will see you then.

The meeting is adjourned.

[Whereupon, at 6:03 p.m., the proceedings were recessed to be resumed at 9:00 a.m., Friday, March 7, 1997.]

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