UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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ORTHOPEDIC AND REHABILITATIVE DEVICES PANEL

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December 9, 2008
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

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JAY D. MABREY, M.D.	Chair, Voting Member
STUART GOODMAN, M.D., Ph.D.	Voting Member
SCOTT EVANS, Ph.D.	Voting Member
BRENT BLUMENSTEIN, Ph.D.	Temporary Voting Member
NANCY OLSEN, M.D.	Temporary Voting Member
HARRY SKINNER, M.D., Ph.D.	Temporary Voting Member
KAREN RUE, R.N., M.B.A.	Consumer Representative
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M E E T I N G

(8:04 a.m.)

DR. MABREY: I'd like to call this meeting of the Orthopedic and Rehabilitation Devices Panel to order.

I'm Dr. Jay Mabrey, the Chairperson of the Panel. I'm also Chair of the Department of Orthopedics at Baylor University Medical Center in Dallas.

At this meeting, the Panel will make a recommendation to the Food and Drug Administration on Supplement 12 of the premarket approval application P940015 for Genzyme's Synvisc-One. This device is indicated for the treatment of pain in osteoarthritis of the knee and patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics, such as acetaminophen.

If you haven't already done so, please sign the attendance sheets that are on the tables by the doors. If you wish to address the Panel during one of the opening sessions, please provide your name to Ms. AnnMarie Williams at the registration table. If you are presenting in any of the open public sessions today and have not previously provided an electronic copy of your presentation to FDA, please arrange to

do so with Ms. Williams.

I note for that record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

I would now like to ask our distinguished Panel members who are generously donating their time to the FDA in the matter being discussed today, and FDA staffed seated at this table, to introduce themselves. Please state your name, your area of expertise, your position and your affiliation. And Ms. George, we'll start with you.

MS. GEORGE: My name's Elisabeth George. I'm from Philips Healthcare, and I am the Vice President of Quality and Regulatory.

MS. RUE: Karen Rue, I'm with the Griswold Special Care. I'm Consumer Representative from Lafayette, Louisiana.

DR. BLUMENSTEIN: I'm Brent Blumenstein, biostatistician based in Washington, D.C., working independently.

DR. SKINNER: My name is Harry Skinner. I'm an orthopedic surgeon. I'm with the St. Jude Heritage Medical Group. I'm formerly a chair of

orthopedics at UC Irvine.

DR. JEAN: My name is Ronald Jean. I'm the Executive Secretary of this Panel.

DR. OLSEN: I'm Nancy Olsen. I'm a physician and a rheumatologist from UT Southwestern Medical Center in Dallas, Texas.

DR. GOODMAN: My name is Stuart Goodman, and I'm a professor of orthopedic surgery at Stanford University in California.

DR. EVANS: Scott Evans, Department of Biostatistics at Harvard University.

MR. MELKERSON: I'm Mark Melkerson. I'm the Director of the Division of General, Restorative and Neurological Devices and the FDA representative of this Panel.

DR. MABREY: And now Dr. Jean, the Executive Secretary of this Panel, will make some introductory remarks.

DR. JEAN: Good morning. I just have a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting. Their telephone number is (410) 974-0947. Information on purchasing videos of today's meeting can be found on the table outside of the meeting room.

Let me take the time to introduce our FDA press contact, Ms. Siobhan DeLancey. Would you please stand? Thank you.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area at any time during the meeting, including breaks. If you are a reporter and wish to speak to FDA officials, please wait until after the Panel meeting has ended. Finally, as a courtesy to those around you, please silence your electronic devices, if you have not already done so.

I will now read into the record three Agency statements prepared for this meeting, two appointment of temporary voting member statements, and the conflict of interest statement.

The first temporary voting member appointment. Pursuant to the authority granted under the Medical Devices Advisory Committee charter dated October 27th, 1990 and amended August 18th, 2006, I appoint the following as voting members of the Orthopedic and Rehabilitation Devices Panel for the duration of this meeting on December 9th, 2008: Dr. Brent Blumenstein, Dr. Scott Evans, Dr. Harry Skinner.

For the record, these people are special

government employees and are consultants to this Panel or another panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. Signed by Dr. Dan Schultz, Director, Center for Devices and Radiological Health, on December 2nd, 2008.

Pursuant to the authority granted under the Medical Devices Advisory Committee charter of the Center for Devices and Radiological Health, dated October 27th, 1990 and as amended, August 18th, 2006, I appoint Dr. Nancy Olsen as a voting member of the Orthopedic and Rehabilitation Devices Panel for the duration of the meeting on December 9th, 2008.

For the record, Dr. Olsen serves as a member of the Arthritis Advisory Committee of the Center for Drug Evaluation and Research. She is a special government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting. Signed by Dr. Randall Lutter, Deputy Commissioner for Policy at FDA, dated November 26th, 2008.

Now I'll read the conflict of interest

statement. The Food and Drug Administration is convening today's meeting of the Orthopedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208, and Section 712 of the Federal Food, Drug and Cosmetic Act, are being provided to participants in today's meeting and to the public. FDA has determined that members and consultants of this Panel are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with these potential financial conflicts, when necessary, to afford the committee essential expertise.

Related to the discussion of today's meeting, members and consultants of this Panel who are special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents, royalties, and primary employment.

For today's agenda, the Panel will discuss, make recommendations, and vote on a premarket approval application supplement for Synvisc-One. The device is indicated for the treatment of pain and osteoarthritis of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics, for example, acetaminophen. Synvisc-One is administered

as a single intra-articular injection.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in connection with this meeting. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Ms. Elisabeth George is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Philips Medical Systems.

We would like to remind members and consultants that if the discussion involves any other product or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue. Thank you.

And just one other announcement. Please note that FDA has no significant orthopedic updates to report since the July 15th, 2008 Panel meeting.

DR. MABREY: Thank you, Dr. Jean. We will now proceed with the open public hearing portion of the meeting. Prior to the meeting, six people requested to speak in the morning and afternoon. We ask that you speak out clearly into the microphone to allow the transcription to provide an accurate record of this meeting. Please state your name and the nature of any financial interest you may have in this or another medical device company. Dr. Jean will now read the open public hearing statement.

DR. JEAN: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of any individual's presentation.

For this reason, FDA encourages you, the open public hearing or industry speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the Sponsor, its product, and if known, its direct competitors.

For example, this financial information may

include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. MABREY: The first open public hearing presenter is Mr. Sean Morris. Mr. Morris, are you in the room?

MR. MORRIS: Yes, I am.

DR. MABREY: Please come to the microphone.

MR. MORRIS: Here or here?

DR. MABREY: Your choice.

MR. MORRIS: Okay. Good morning. My name is Sean Morris and I'm from the law firm of Miles and Stockbridge. I have no financial interest in the product being discussed today or its sponsor. I speak here today representing the Orthopedic Surgical Manufacturers Association.

OSMA, a trade association with over 30 member companies, welcomes this opportunity to provide general comments at today's Orthopedic

Advisory Panel meeting. OSMA's comments should not be taken as an endorsement of the product being discussed today. We ask instead that our comments be considered during today's Panel deliberations. These comments represent the careful compilation of the member companies' views.

OSMA was formed over 45 years ago and has worked cooperatively with the FDA, the American Academy of Orthopedic Surgeons, the American Society for Testing and Materials, and other professional medical societies and standards development bodies. This collaboration has helped to ensure that orthopedic medical products are safe, of uniform high quality, and supplied in quantities sufficient to meet national needs.

Association membership currently includes over 30 companies who produce over 85 percent of all orthopedic implants intended for clinical use in the United States. OSMA has a strong and vested interest in ensuring the ongoing availability of safe and effective medical devices.

The deliberations of the Panel today, and the Panel's recommendation to the FDA, will have a direct bearing on the availability of new products. We make these comments to remind the Panel of the

regulatory burden that must be met today. We urge the Panel to focus its deliberations on the product's safety and effectiveness based on the data provided.

The FDA is responsible for protecting the American public from drugs, devices, food and cosmetics that are either adulterated or are unsafe or ineffective. However, FDA has another role: to foster innovation. The Orthopedic Devices Branch is fortunate to have available a staff of qualified reviewers, including a board-certified orthopedic surgeon, to evaluate the types of applications brought before this Panel.

The role of this Panel is also very important to the analysis of the data in the manufacturer's application and to determine the availability of new and innovative products in the U.S. marketplace. Those of you on this Panel have been selected based on your expertise and training. You also bring the view of practicing clinicians who treat patients with commercially available products.

OSMA is aware that you've received training from FDA on the law and the regulation, and we do not intend to repeat that information today. We do, however, want to emphasize two points that may have a bearing on today's deliberations: (1) reasonable

assurance of safety and effectiveness; and (2) valid scientific evidence.

Point 1, reasonable assurance of safety and effectiveness. There is reasonable assurance that a device is safe when it can be determined that the probable benefits outweigh the probable risks. Some important caveats associated with this over-simplified statement include valid scientific evidence and proper labeling, and that safety data may be generated in a laboratory, in animals or in humans. There is reasonable assurance that a device is effective when it provides a clinically significant result. Again, labeling and valid scientific evidence play important roles in this determination. The regulation and the law clearly state that the standard to be met is a reasonable assurance of safety and effectiveness. Reasonable is defined as moderate, fair and inexpensive.

Point 2, valid scientific evidence. The regulation states that well-controlled investigations shall be the principal means to generate the data used in the effectiveness determination. The following principles are cited in the regulation as being recognized by the scientific community as essentials in a well-controlled investigation: (1) a

study protocol; (2) method of selecting subjects; (3) method of observation and recording of results; (4) comparison of results with a control.

The Panel has an important job today. You must listen to the data presented by the Sponsor, evaluate the FDA presentations, and make a recommendation about the approvability of the Sponsor's application. We speak for many applicants when we ask for your careful consideration. Please keep in mind that the standard is a reasonable assurance, balancing the benefits with the risks. The regulatory standard is not proof beyond a shadow of a doubt.

When considering making recommendations for further studies, remember that FDA takes these recommendations seriously, often as a consensus of the Panel as a whole, and they may delay the introduction of a useful product or result in burdensome and expensive additional data collection. Therefore, you play an important role in reducing the burden of bringing new products that you and your colleagues use in treating patients to the market.

Please be thoughtful in weighing the evidence. Remember that the standard is a reasonable assurance of safety and effectiveness and that there

is a legally broad range of valid scientific evidence to support that determination.

OSMA thanks the FDA and the Panel for the opportunity to speak today. Our association trusts that its comments are taken in the spirit offered, to help the FDA decide whether to make a new product available for use in the U.S. marketplace. Thank you.

DR. MABREY: Thank you, Mr. Morris. Is Ms. Mary Lou Gundersen present? Mary Lou Gundersen?

(No response.)

DR. MABREY: Not seeing her, I'll proceed to our next speaker, Ms. Diane White. Is Ms. Diane White available?

(No response.)

DR. MABREY: Not seeing any hands going up, we'll proceed to the next speaker. Is Dr. Andrew Spitzer in the room?

DR. SPITZER: Yes.

DR. MABREY: Come on forward.

DR. SPITZER: Good morning, Mr. Chairman, ladies and gentlemen. Thank you for the opportunity to speak at this Panel meeting. In the interest of full disclosure, I would like to share that I am a paid consultant of and have done research sponsored

by Genzyme Biosurgery. However, I have come here today completely on my own time, without any compensation whatsoever from any person or company, in order to share my thoughts about the potential benefits of a single-injection viscosupplement.

My name is Andrew Spitzer. I'm a practicing orthopedic surgeon specializing in joint replacement of the hip and knee and the outpatient management of osteoarthritis of the hip and knee. Since 1993, after finishing my residency in orthopedic surgery at the University of Pennsylvania and my fellowship in reconstructive surgery at Harvard's Brigham and Women's Hospital, I have been affiliated with the Kerlan Jobe Orthopedic Clinic in Los Angeles, California, and I have recently been appointed director of the Joint Replacement Institute at Cedars-Sinai Medical Center, also in Los Angeles.

I perform approximately 250 total joints per year and evaluate an additional hundred office patients per week, with osteoarthritis of the hip or knee. Throughout my career, it has been ever more apparent to me that while the outcome of knee replacement surgery can be outstanding, not every patient with an arthritic knee is ready for, desires to undergo, or is a candidate for knee replacement.

Preserving function for patients with arthritic knees, in a nonoperative manner, has always been a priority in my practice. As a result, I am an enthusiastic user of viscosupplements for this purpose. It is well known that only approximately 10 percent of patients who carry a diagnosis of knee osteoarthritis, and are potential candidates for total knee replacement, actually have the surgery. And April 2007 study published in the American *Journal of Bone and Joint Surgery* projects that by the year 2030, the current annual volume of 450,000 total knee replacements performed in the United States is expected to rise to 3.48 million.

This astounding number will surely strain the human and economic resources available to manage these patients and their surgeries, but even more daunting is the fact that 10 times the number of patients, nearly 35 million Americans, will need an alternative treatment for symptomatic knee osteoarthritis.

Knee osteoarthritis is already one of the leading causes of disability among the workforce and is expected to contribute even greater numbers as the population ages. And furthermore, the economic impact of this disease is staggering, with some

estimates exceeding a hundred and twenty billion dollars spent annually on its treatment. This financial burden and huge projected volume of patients, added to an already strained healthcare system, with long waiting times to obtain care from a physician, mandate better, more efficient, and more effective management strategies for those who suffer with this painful and debilitating condition.

Currently, the nonsurgical treatment of knee osteoarthritis consists of the judicious use of oral analgesics, nonsteroidal anti-inflammatory drugs, physical therapy, bracing, and occasional intra-articular corticosteroid injections. The relative lack of adequate efficacy of these options results in an inability of patients to exercise further deconditioning of their lower extremities and worsening of the osteoarthritic symptoms.

The advent of viscosupplementation has significantly improved our ability as physicians to more effectively manage knee osteoarthritis; it is a local treatment, avoiding systemic complications and reducing the need for systemic, potentially harmful or addicting medications. It can reliably provide sustained pain relief and improvement in function for up to six months and, in some anecdotal reports, even

longer. And it has indeed become a mainstay in the armamentarium of tools used to treat painful knee osteoarthritis. However, it requires three to five weekly injections.

Recent data presented at the meetings of the European League Against Rheumatism and the Osteoarthritis Research Society International suggested a six cc injection of Synvisc. A single injection is effective in providing up to six months of symptomatic relief from painful knee arthritis.

I believe you will hear much more about this from the Genzyme representatives during the day, and I will not comment further on the merits of the data, though I believe it to be quite compelling. I do want to emphasize, however, the revolutionary effect that the availability of such a product would have on my practice in particular, on the healthcare system in general, and most importantly, on patients who suffer from painful osteoarthritis of the knee.

A single-injection viscosupplement would virtually eliminate the backlog of patients waiting to see me in the office. It would dramatically increase my ability to efficiently and safely manage my patients, and it would facilitate me providing care to the growing number of patients requiring

management for their osteoarthritis.

As an illustration of the numbers, I have a modest volume of roughly 20 injection visits out of the hundred total weekly visits to my office. In a three- to five-week period, these 20 patients will receive 60 to a hundred injections. If a single-injection viscosupplement were to become available, the number of total injections for this same time period would be reduced 66 to 80 percent, and the overall number of available patient slots would be increased by 17 to 20 percent. Multiplying this effect by the multitude of similar physician practices which care for patients with knee osteoarthritis, the increased capacity for care is dramatic and should result in less wait time for patients to gain access to the system, a larger overall number of patients seen, and in my opinion, a major improvement in the healthcare system's ability to appropriately and effectively care for this important and growing segment of our population.

Most importantly, as I have emphasized, a single-injection viscosupplement would be a boon for patients. It would reduce the time commitment required to obtain their treatment to a single office visit. It would also spare them the discomfort of

two to four additional injections and the corresponding risks of local reaction, additional pain, disability, loss of function and time out of work.

Finally, assuming the single injection provides a similar duration of action and a similar reimbursement structure, the reduction in the number of injections would have significant -- would save significant dollars for the patient and for the healthcare system at large.

In summary, viscosupplementation is an extremely valuable, safe, and effective treatment option for patients who suffer from painful knee osteoarthritis. The current requirement for three to five injections is a physical and economic burden for patients. The availability of a single-injection viscosupplement would revolutionize the ability of the healthcare system to provide this therapy to the rapidly growing population of candidate patients in a time and cost-effective manner and with greater safety and less discomfort.

I urge you on behalf of my patients, who will benefit immensely from a single-injection viscosupplement, to approve the use of this product. Thank you for your time and attention.

DR. MABREY: Thank you, Dr. Spitzer. Is there anyone else who would like to come forward?

(No response.)

DR. MABREY: Not seeing any hands, we'll proceed with today's agenda. Please note that there will be a second open public session in the afternoon. We will now proceed to the Sponsor presentation for Genzyme Synvisc-One.

I would like to remind the public observers at this meeting that while this meeting is open to the public for observation, public attendees may not participate except at the specific request of the Panel. The Sponsor will introduce the speakers. You have 90 minutes.

MR. HALPIN: Thank you, Dr. Mabrey. Good morning. My name is Mike Halpin. I'm Vice President of Regulatory Affairs at Genzyme Corporation, and on behalf of Genzyme, I would like to thank the Panel and the FDA for the opportunity to present the clinical trial results of our product, Synvisc-One. I'd also like to point out that Synvisc-One is not a new product but a modification to our currently approved viscosupplement, Synvisc.

The agenda is up on the slide, and I'll start with a brief introduction. After that, we'll

go through an overview of the OA treatment and clinical research methodology for OA pain products, go through the clinical study results for Synvisc-One as well as the statistical considerations used in that clinical trial. After that, we'll hear an expert report on the clinical meaning in an OA pain setting and how to interpret that, followed by an expert opinion on the clinical trial results for Synvisc-One. And I will follow with brief concluding remarks.

I just wanted to take a moment to point out and introduce the external experts that we have with us this morning. Dr. Robert Dworkin is a professor of anesthesiology, neurology, oncology, and psychiatry at the University of Rochester School of Medicine and is an expert on the study of pain and interpretation of pain endpoints from clinical studies. Today, he will present on his experiences with studying and interpreting endpoints in clinical trials.

We also have Dr. Lee Simon, who is an Associate Clinical Professor of Medicine at Harvard Medical School and Beth Israel Deaconess Medical Center and was a former Division Director within CDER at FDA, and he will provide an expert opinion on

Synvisc-One.

Dr. Ralph D'Agostino is a professor of mathematics, statistics, and public health at Boston University and a respected and widely published statistician with over 30 years of experience in running clinical trials and epidemiological research. He's also been a consultant to the Food and Drug Administration since 1974, serving on a number of drug and device advisory committees.

Finally, Professor Chevalier is a professor of rheumatology at the University of Paris XII and is currently head of the department of rheumatology at Henri Mondor Hospital in the Paris area. He is a published expert in the field of OA and rheumatology and was one of the senior investigators in a pilot and pivotal Synvisc-One clinical study. Both Dr. D'Agostino and Professor Chevalier will be available for Advisory Panel questions.

I'd like to start with a brief introduction which will include looking at the viscosupplementation products available in the U.S., followed by a brief description of the Genzyme viscosupplement product, Synvisc, and the modifications required to create Synvisc-One. I'd also like to briefly discuss the advice that Genzyme

used in designing the Synvisc-One pivotal trial.

Viscosupplementation in the U.S. is a local treatment injected into the intra-articular joint space of the knee. These are HA-based products using hyaluronic acid, and they provide pain relief for knee OA. There's no function or mobility claims in the indications for use. The indicated use is for patients who fail to respond adequately to conservative nonpharmacologic therapy and simple analgesics, such as acetaminophen. Typically, these products require three to five weekly injections, with 2 to 2½ mL's being injected at each treatment.

There are currently five products available in the U.S., and as you can see, all of these are available only for the knee. The years of approval range from 1997 to 2004, the number of injections range from three to five, and the duration ranges from 26, and then, more recently, there are some products that have been improved, with 22 and 12 weeks of duration.

Synvisc has been commercially available for 16 years and was approved by the FDA in 1997. It's currently available in over 70 countries, and over four and a half million patients have been treated with Synvisc, with over 13 million Synvisc injections

performed, and there's been a very low reported rate of serious related AEs.

Synvisc-One is a modification of Synvisc, in order to allow a single injection. It involves a simple change to packaging and instructions for use, and the indication for use would be the same for Synvisc and Synvisc-One. If you look at this chart, it compares some of the characteristics of Synvisc and Synvisc-One, and you can see that they both have the same hylan G-F 20 HA material. Synvisc has two mL's of this in each syringe, whereas Synvisc-One would have six mL's. There would be three injections of Synvisc, in order to create a full treatment, and those are each spaced a week apart, whereas Synvisc-One would be a single injection given on the first day of the first office visit. However, I wanted to point out that the total volume is actually the same for Synvisc and Synvisc-One, and that's six mL's of hylan G-F 20.

And this is just a picture that shows Synvisc on the left and then you can see Synvisc-One on the right, as a single-injection format.

The proposed indication for Synvisc-One would be the same as Synvisc, in that it's indicated for treatment of pain in OA of the knee in patients

who failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics, such as acetaminophen.

The FDA has, in their Panel pack, described that they did not actually get a chance to look at the final design of the Synvisc-One pivotal trial. And I just wanted to point out that both the Synvisc pilot study and the Synvisc-One pivotal trial were European studies and were done outside the U.S., so we did not file an IDE with the FDA. I also want to point that, at the time we were doing these studies, we also had two other viscosupplements that were ongoing in the U.S. that were the subjects of IDEs with the FDA, and that actually gave us three opportunities to interact with the FDA and get advice on clinical trial design. The first two opportunities would be for the IDE designs of these viscosupplement trials, and I just want to point out that WOMAC A, repeated measures over 26 weeks, was the primary endpoint for both of these studies. And then I also wanted to point out that, following the pilot study, we had a meeting with the FDA to sit down and seek their advice on what to incorporate into our Synvisc-One pivotal trial design.

This slide briefly reviews what we actually

put into the trial design for the pivotal study, so based on the U.S. IDE trials, WOMAC A as a primary endpoint, using repeated measures rather than using a landmark analysis technique. And then, following our meeting with the FDA to discuss the pilot review results and what potentially might be a design for the pivotal trial, we determined that an additional clinical trial would be required and that should be a double-blind design. And then, rather, comparing directly to Synvisc, the FDA preferred that we would use a saline control comparator.

There is some initial experience outside the U.S. with Synvisc-One. Synvisc-One has been approved in the EU and has also been approved in additional countries outside the U.S. To date, we have approximately 10,000 patients who have been treated with Synvisc-One and no serious related adverse events have been reported to date.

So at this time, I'd like to introduce Dr. Richard Polisson, who will discuss OA pain treatment options and methods for clinical research related to OA pain products. Dr. Polisson is a rheumatologist by training and former clinical director of the arthritis unit at Massachusetts General Hospital and Harvard Medical School.

Dr. Polisson continues to actively see rheumatology patients in a weekly session. Thank you.

DR. POLISSON: Good morning. So my role today will be threefold, to review osteoarthritis as a disorder and to talk about current therapies. Now, I know many of you are experts in this field and see patients in this area, so my comments will be very high level and intended only to frame the debate that you'll hear throughout the day today and into the afternoon.

I'll make a few comments, then, on viscosupplements and how they fit into the treatment paradigm for OA, and then finally end up with a little speech on clinical trial methodology in OA pain and with a particular focus on the endpoints that we used in this particular program. So this is not new, everybody knows this, OA is common, looking around the room here, and I suspect that many of you probably have OA, radiographic OA, and if you don't have it, you'll probably get it. But the real culprit here is symptomatic OA. It's what brings the patient to the doctor.

Twenty-seven million Americans have symptomatic OA in any joint, and this represents an increase of six million patients entered into the

decade 1995 to 2005, so people are being added to the roll, so I thought this fact was quite astounding. So this program is growing by orders of magnitude.

It's local disorder, so we feel that it's particularly amenable to local therapy. And the -- type of OA is pain, pain expressed by walking and by ambulation, and this is the thing that we're going after today. This product that's under review before you is really intended to ameliorate pain in symptomatic OA patients.

So this is the current treatment algorithm for OA. It's a very simple cartoon, probably oversimplified for those of you in the know, but it provides talking points, anyway. And I think that, at the baseline, of course, we try to do the best we can about patient education, having them lose weight or maintain their weight, asking them to embrace physical medicine modalities like physical therapy and exercise. And then, usually at the same time, because they're symptomatic and in the office, we oftentimes ask them to begin taking acetaminophen in doses up to four grams per day.

Now, historically, we'd always been told and taught in medical school that acetaminophen was remarkably safe. But I think that recently we've

become sensitized to the issue of hepatotoxicity, primarily in patients who are taking or using alcohol concomitantly, and the cardiovascular risk with regular users is really not trivial at all.

Finally, the next group deserves a little comment here. These are anti-inflammatory drugs, either in over-the-counter dosages or full prescription NSAIDs, to include the only coxib left on the market, that being Celecoxib. And these drugs have been in the media, have been in front of us now for five years, and it's no surprise they're absorbed in the small bowel and metabolized in the liver, excreted in the kidney, and they're highly bound to plasma proteins, and so they have lots of side effects that we know of, and lots of medication interactions, particular Coumadin. And we've been very, very sensitized to the cardiovascular risk, and this is vexing because most patients with OA are in that age range where cardiovascular risk is a concern.

And finally, at the end, we heard Dr. Spitzer talk, in the open session, about total joint replacement surgery. I know many of you do this procedure in your own practice. This is an amazing procedure. No one is doubting the

effectiveness of this procedure. It's the biggest advance in the last 60 years in managing serious arthritis patients. But it is invasive, it's a big deal, and it's primarily indicated for end-stage patients who have unrelenting pain, together with structural problems.

So there are many symptomatic patients out there. There's a big gap who are not candidates for total joint replacement but continue to have symptoms, either because they can't take NSAIDs or won't take NSAIDs or they're just not in the age range where total joints -- a total joint replacement is feasible or allowable. And then, along the side here, I think you see the local therapy is intra-articular steroids, HA-based viscosupplements, and topical NSAIDs. I think they have their downside as well. Viscosupplements in particular, with three to five injections being the typical course, that's a real nuisance for patients and it's an impediment to care.

A couple comments here about viscosupplements. Without going into a 45-minute lecture, based on net analyses such as Zhang and The Cochrane and a concept called effect size that allows us to compare how good drugs are across trials and

across indications, viscosupplements offer comparable pain relief to the oral therapies that I've just defined and are certainly superior to placebo.

And because they're local, the use of them might avoid the toxicity and the associated cost of systemic therapy that I defined on the previous slide. And we believe that it's a critical option if there are contraindication to patients taking anti-inflammatories or that they're just not ready for total joint replacement. And finally, based on the evidence and the literature, both for efficacy and safety, this particular class of treatment has been recommended by major professional societies in rheumatology, orthopedics, and pain.

I'd like to switch gears here now and talk a little bit about clinical trials in OA. And I've done clinical trials for 28 years, first at NIH, then at Duke, then at Mass. General, and now here at Genzyme, and I can tell you, this is a really tough area, and it's tough primarily because of some of the features noted on this slide.

So with respect to the population, OA patients are heterogeneous. There are cycles of pain that are punctuated by periods of relatively low pain intensity. And so measuring oscillations like this,

over time, between a treatment group and a control group is very, very challenging.

Because patients who have OA tend to be aged, we are now confronted with comorbid diseases. So many folks have hypertension, coronary disease, obesity, lung disease, and it's well known that these comorbid conditions can adversely impact the patient with respect to their perception of OA pain. And with these diseases come the concomitant medications that oftentimes make enrollment of a great patient and a valuable patient into an OA trial very difficult.

Finally, with respect to the trial design itself, the placebo control is almost uniformly large. It is to be expected. It is the rule rather than the exception. And, in addition, there are other control group issues to keep in mind here, especially with the local therapy. With the control group, oftentimes we perform arthrocentesis, so the mere act of putting a needle into someone and taking fluid out could be expected to have an ameliorating effect on a patient's pain.

Because trials like this oftentimes go six months and because there's a placebo group or a control group, we oftentimes have to use rescue

medication, but we feel that it too is a problem in terms of analysis because it probably blunts the ability to differentiate between control and the active therapy.

One final thing to comment on and that has to do with any procedurally administered OA product, and that is that if it's a local therapy, it should be expected to treat the signal joint only, and that's in contrast to an anti-inflammatory trial, in which case, the anti-inflammatory, since it's systemic, might be expected to have some effect on all osteoarthritic joints to some degree or another.

And finally, the endpoints used to measure OA are subjective, and I'm about to dive into that right now. So we're talking here about patient-reported outcomes, and I'd like to bundle these into my first point here. We use WOMAC, which stands for the Western Ontario McMaster University Osteoarthritis Index. It is validated and widely used in osteoarthritis clinical research, and in osteoarthritis product development, it measures three domains, pain, stiffness and function. We're focusing today primarily on pain. It is measured by asking the patient five questions, and then they score those questions. We measured function, but in

this particular application to the FDA, we're not interested in a claim for function.

In addition to this, we also ask the patient and the blinded observer how the patient is doing. It's a global assessment. With respect to the PTGA, we feel very strongly about this since this is so patient-centered. It really is the face value of asking the patient. This should be so evident to those of you who continue to see patients.

Finally, we did do some responder analyses, a one-responder, which you'll hear about, OMERACT-OARSI responder. At the time we were designing this trial, we had very little experience in how these endpoints might behave in a viscosupplement trial, and in addition, we're not aware that any of these have been used as a primary basis of approval of any OA product, and because of that, we included them as secondary endpoints only.

Drilling down now into WOMAC A, which really is going to be -- you'll hear about this for the rest of the day. WOMAC A focuses on pain. There are five questions, and a patient is asked the following. And please think about this and think about a how a patient receives this. So what was your level of pain over the last 48 hours while

walking on a flat surface, going up or down stairs, at night while in bed, sitting and lying, or standing upright? That is WOMAC A, the total WOMAC scale.

WOMAC A1, in my opinion, deserves a special comment here. It asks the patient about how much pain they have while walking on a flat surface. It's exactly the question that most people ask the patient when they escort them in from the waiting room into the office. Are you having pain while you're walking, and if so, how much? That is WOMAC A1.

A1, in addition to its analog, the visual analog scale for walking pain, the two of them together have been used as the primary basis of approval of most OA products. So that's point number one. Point number two is, in our opinion, we feel that this represents a most relevant measure for patients on the mild to moderate end of the OA continuum. Those were the patients that we wanted in our trial. If you look at Questions 3 and 4, having pain at night while in bed or while sitting or lying, to us, anyway, really reflect a more relevant measure for patients who are on the more severe or extreme end of the continuum.

Regardless of this, we chose WOMAC A as our primary endpoint, as Mike Halpin mentioned, based on

the deliberations that we had with FDA on our other IDE studies, despite the fact that we still favor A1 as probably the best way to measure outcome in this disease, with these types of patients.

My summary slide is this: OA is challenging to treat and to study. The NSAID rofecoxib catastrophe really complicated patient management, and we see a shrinking number of options, and we don't like to see that with a growing problem. We need more options. OA clinical trials use subjective patient-reported outcomes. It's our belief that the bundled WOMAC A, A1, and patient global really reflect clinical benefit.

And finally, viscosupplements are an effective and safe local treatment for OA. They obviate the potential exposure at issue with the NSAIDs, and they are recommended by multiple professional societies.

So that's the end of my speech today, and I'd now like to introduce Dr. Lena Holmdahl, who's Vice President of Clinical Research. Lena has worked with me for five years, and she will present the details regarding the safety and efficacy of our Synvisc-One trial. Dr. Holmdahl.

DR. HOLMDAHL: Mr. Chairman, dear Panel

members, ladies and gentlemen, my role today is to give you an overview of the clinical development of Synvisc-One. I'd like to start off with an overview of my presentation. I will present why we undertook this development, how we did it, what we found, and what we have concluded.

The currently approved Synvisc is dosed two times at two milliliters, injected three times with one week between each injection. In having Synvisc on the market for quite some time, we received requests from physicians and from patients for a simplified treatment regimen, and we were also aware that physicians were experimenting with a simplified treatment. We therefore believe it would be the responsible thing to do to investigate if it was possible to have a simplified treatment.

This part is intended to give you an overview of the decision making leading up to the trial and to the trial itself. We started by conducted a pilot trial. The two variables that potentially could be changed were the number of injections and the injected volume, so we designed a pilot trial to try out various combinations of the two, in a randomized prospective, open-label study including 100 patients.

One treatment was the currently approved treatment with three injections of two milliliters of Synvisc. This was used as the comparator. There were three arms with different combinations of a four mL treatment, and the fifth arm was a one-time injection of six mL. Safety was assessed by collecting adverse events, and efficacy was assessed using commonly used patient-reported outcomes as just described to you by Dr. Polisson.

The key findings from this pilot trial was all treatments were safe, all were efficacious, but there seemed to be some differences in terms of degree of efficacy. So what we did was to select the dose to move forward, was that we ran all the treatment options based on the performance relative to the efficacy endpoints, WOMAC A1, PTGA and COGA, and also on their performance and safety.

And the conclusion of that was that the one-time six mL treatment performed as good as, if not better than, the currently approved treatment. And moreover, it fulfilled the criteria for simplification; a patient will get all three treatments in one. We also knew that commonly used and validated endpoints in OA trials are reported by the patients, and to be able to do a high-quality

study, patients and caregivers, therefore, had to be blinded.

Since both the volumes, the number of injections for the one-time six mL or the three times two mL treatments were different, we identified two scenarios to maintain blinding. If we were to compare it to the currently approved treatment, we had to add arthrocentesis and intra-articular injections at two occasions in the one-time six mL.

Moreover, we were concerned about additional intra-articular interventions without apparent benefits to patients, concluded that this option was less attractive and therefore chose to compare it to saline, which we thought would make the overall study design much cleaner. Saline had also been recommended by the FDA during previous trial design discussions for other OA trials that we have carried out.

We therefore designed multicenter, randomized, parallel group control trials where patients and observers were blinded. And for the reasons mentioned, we choose arthrocentesis and saline injection as the comparator to maintain the blind. Furthermore, the study was designed and conducted according to GCP, Declaration of Helsinki,

International Committee on Harmonization, and all applicable local laws and regulations. These requirements are consistent with the regulatory criteria for valid scientific evidence.

The target was to include patients with mild to moderate disease since they are likely to benefit from this kind of therapy. The patients should meet the American College of Rheumatology criteria for primary OA in the knee. This means that they should have had knee pain associated with radiographical or other well-defined signs and symptoms of OA.

The severity of the pain on walking should be moderate to severe pain, which is the same as a score of two to three on WOMAC A1, and an average score of 1.5 to 3.5 on the WOMAC A scale. They should, furthermore, be ambulatory, with an active lifestyle and in good general health.

Exclusion criteria included end-stage disease, secondary OA and factors that in general terms either could constitute a risk to the patient or could confound results. An example of a factor that could confound results is symptomatic OA of another joint in the lower limbs that was not responsive to rescue medication. This also means

that a patient with symptomatic OA in the contralateral knee or in either hip could be included as long as the pain responded to acetaminophen at the time of inclusion.

This slide shows the three phases of the study. The purpose of the screening phase was to enable inclusion -- enable the evaluation of inclusion/exclusion criteria and to enable washout of prohibiting medications. This was followed by an initial phase, which was the phase where we evaluated safety and efficacy. This phase included the randomization, the treatment, and the follow-up for 26 weeks, for safety and efficacy evaluations.

After completion of this initial phase, the patient could enter into repeat treatment phase. The purpose of this phase was to ensure that repeat treatment was safe, and only safety was evaluated.

The primary efficacy objective was to demonstrate that a one-time six mL injection of Synvisc provides superior pain relief on the WOMAC A Likert scale, over 26 weeks, as compared to a one-time six mL intra-articular injection of saline. Secondary efficacy objectives were meant to be supportive. They were to analyze the differences between the WOMAC A1 sub-score in the two groups, the

patient global assessment, the clinical observer global assessment, and WOMAC A, at the end of the trial, as well as WOMAC C and to do an OMERACT-OARSI responder analysis. As indicated in this table, several of the secondary endpoints were assessing various aspects of pain. All analyses were to be done on the intent to treat population as defined as all patients randomized.

In the design of the trial, we worked closely with our biostatisticians on the statistical aspects of the trial. Their recommendation was to use a repeated measures analysis of covariance, which they thought was appropriate in this setting. This is a standard and well-accepted way of analyzing this kind of data. We also knew that FDA that they had recommended this approach in other trials we had done.

The models were to include terms for treatment, site, visit, and visit-by-treatment interaction, and the baseline WOMAC subscale A score as a covariant. There are likely several other options that could have been used, but we decided to follow this recommendation. Importantly, we adhered to this decision made beforehand. We did not change the protocol, we did not do an -- analysis, and we

did not change the statistical analysis plan. The analyses were there for pre-specified in the statistical analysis plan prior to -- prior to looking at the data and prior to un-blinding the data.

There were three different types of outcomes in the study. We therefore pre-specified, in the statistical analysis plan, three different statistical models to analyze the data. They are summarized in this slide. Ordinal endpoints, that is, WOMAC A1, PTGA and COGA, were analyzed using generalized estimating equations for proportional odds logistic regression.

The continuous endpoints, WOMAC A at 26 weeks, and WOMAC C, were analyzed using repeated measures, ANCOVA. Binary endpoints collected over time, for example, the proportional WOMAC A1 responders, were analyzed using generalized estimating equations for binary response logistic regression. These analyses were pre-specified in the statistical analysis plan prior to un-blinding of data.

Patients stayed in the study and a very few discontinued. In the Synvisc arm, 93 percent completed the study, and in the control arm, 91

percent completed the study. There is therefore a high degree of completeness in the data set and few missing values. We therefore believe that the study is of a high quality. This slide shows the baseline demographics. It shows that the two groups were comparable and, thus, that randomization worked. Importantly, WOMAC A1 score was comparable between the two arms at baseline. It is worth noting that the mean age is 63 years. This means that many patients were in an active age and many were still in the active workforce.

Moreover, it shows that the patient population is representative of patients with mild to moderate OA. For example, the MI and gender distribution is what you would expect. We therefore believe that the study population is a fair representation of the general population of OA patients with mild to moderate disease, regardless of geographical location.

The next part of the presentation focuses on the efficacy results. All analyses were done on the ITT population. We also undertook analyses on the protocol population, and these analyses were supportive of the ITT results.

The primary efficacy objective was to

demonstrate that a one-time six mL injection of Synvisc provided superior pain relief, measured on the WOMAC A, on the Likert scale, over 26 weeks, as compared to saline. This objective was met. And this is how the results look if you see them in the table. In the difference from control column, a negative number would favor Synvisc. The difference from baseline is shown in this column over here, where a minus 83 in the Synvisc arm compares to a minus 0.69 in the control arm, leads to the difference from control.

Synvisc provided greater pain relief than saline over the duration of the trial. The P value is 0.047 and the effect size is 0.23. This is in the same range as other products used to treat OA pain, as you will hear more about from Dr. Simon later in this presentation.

You will see that the FDA has asked us to analyze the primary efficacy endpoint, as well as secondary endpoints, differently. All of these analyses were done post hoc, when the results were available to the FDA.

This graph illustrates the same results of the primary efficacy endpoint, as I showed in the previous slide. As shown, Synvisc was superior to

the control treatment for the duration of the trial. You might be used to seeing a landmark analysis at a certain time point. Here we have analyzed difference over time, which is consistent with what we have been advised by the FDA for other trials. A reeducation in OA pain is what we propose to have in our indications for use. We also believe it is important to put this in the patient perspective. The patient would experience a change from baseline and not compare him or herself to a control. The change from baseline in WOMAC A pain score is 36 in the Synvisc-One arm. This is highly statistically significant.

Another way of looking at this is that the change from baseline in the Synvisc-One arm is approximately one point on the Likert scale. It is also noteworthy that a change from baseline is commonly used to evaluate pain management, as you will hear more about from Dr. Dworkin later in this presentation.

This slide gives an overview of the primary and the secondary endpoints analyzed the way it was specified in the statistical analysis plan, and we will do it. As you can see, in addition to the primary efficacy endpoint measuring pain over time, several secondary endpoints also measured various

aspects of pain.

Importantly, the various pain-related outcomes were statistically significant, including WOMAC A1, PTGA and COGA, both over time and at the end of the trial. OMERACT-OARSI responder analysis trended in the same direction. This table also lists the effect sizes for the various endpoints shown here. These effect sizes are comparable to other products indicated for OA pain, as you will hear more about later on.

In addition to the primary efficacy graph, this is one of the most important graphs in the presentation. This graph shows the odds rations for all categorical secondary endpoints. This is a common way to express treatment effect for categorical values. On the Y axis is plotted odds ratios, 95-percent confidence intervals for odds ratio.

The blue hash line crosses one, which is the value where there would be no difference between two study groups. Any odds ratio greater than one, that is above the hash line, would favor the control treatment, and any odds ratio less than one would favor Synvisc treatment.

If the arrow bars represent -- the 95-

percent confidence interval do not cross one, the difference is statistically significant at the five-percent level. All of the odds ratios were consistently below one, indicating a superior outcome with Synvisc treatment.

To the far left is plotted the odds ratios for the WOMAC A1, for the duration of the trial, and next to that the odds ratio for WOMAC A1 at the end of the trial. WOMAC A1 is a commonly used outcomes measure in OA trials and has been the basis for U.S. approval of several products.

The treatment with Synvisc resulted in a statistically significant reduction in WOMAC A1 odds ratio to 0.64, over the 26 weeks, and an odds ratio of 0.56 at the end of the trial. This means that a patient who received Synvisc-One was twice as likely to have reduced pain on walking, both for the duration of the trial and at the end of the trial. Hence, the effect was still present after six months.

Not surprisingly, this translated into a significant reduction in the odds ratios for PTGA, both for the duration of the trial and at the end of the trial. The odds ratio was 0.69 and .059, respectively. This means that the patients were twice as likely to assess themselves better if

treated with Synvisc-One.

The COGA was almost identical to the PTGA, and in essence, this confirms the patients' assessment. They did not only rate themselves as better, a clinical observer made the same assessment. It is important to note in this context that both the patient and the clinical observer were blinded to study treatment. The odds ratio to the far right illustrates the results from the OMERACT-OARSI responder analysis for the duration of the trial and at the end of the trial. In addition to measuring pain, this responder analysis includes aspects of function as well. The results favor Synvisc. Both of the odds ratios are below one. But as evident from the arrow bars, the difference did not reach statistical significance at the five-percent level.

Another way to see the effect is to analyze the use of rescue medication. In this study, acetaminophen was allowed to control joint pain, as it would be very difficult to conduct a trial with a duration of six months without allowing for some kind of pain control, in particular in the control arm. However, the dilemma this creates is that it also can reduce the difference between the two study groups.

This graph shows the average daily

consumption of rescue medication in the two groups. Starting at week eight, the two curves began to separate, trending in favor Synvisc-One. However, this difference did not reach statistical significance for the duration of the trial.

In reality OA typically is not a single joint disease but can affect multiple joints. Patients with OA in another lower limb joint were allowed to enter into the study as long as the pain was responsive to acetaminophen. However, during the course of the study, OA in other joints can be more or less symptomatic. Synvisc is not a systemic treatment. It is a local treatment and has the effect in the joint in which it is injected. It cannot be expected to have an effect in other joints.

However, even with the best intent and well-established outcome measures, it can be difficult for patients to differentiate where the pain comes from. We were therefore aware that OA in other lower limb joints possibly could confound results, and we had therefore pre-specified a covariant to be able to address this.

These two graphs show the WOMAC A pain scale in all patients shown here and in patients without symptomatic OA in another lower limb joint

shown here. As evident, the separation from control treatment is much larger on the WOMAC A pain scale if the treated joint is the only joint affected. In this group, the difference from baseline is 43 percent in the Synvisc arm, and the difference is highly statistically significant. WOMAC A1 pain on walking is commonly used outcome measure for OA and highly relevant in patients with mild to moderate disease. To further understand the results, we did a WOMAC A1 responder analysis. In this analysis, a responder was defined as a patient who improved by at least one category on the Likert scale, that is, for example, from severe to moderate, and who did not withdraw due to lack of efficacy.

The responder rates for the two arms is shown in this graph. The curves start to separate already the first month after treatment, and at week 18, 71 percent of the patients in the Synvisc arm were responders, compared to 54 percent in the control arm. This difference is highly statistically significant. The separation between treatment and control persisted to the end of the trial. This means that there still was an effect half a year after one injection of Synvisc.

To conclude this part of the presentation,

one injection of Synvisc-One was superior in reducing OA pain over 26 weeks. The primary objective of the study was therefore met. From a patient perspective, this translated into a significant reduction in OA pain, compared to baseline, a greater proportion of patients who had a reduced pain on walking in the Synvisc-One arm, that patients were more likely to feel better in the Synvisc arm, and they were more likely to be rated as better by blinded observers. We therefore believe that these results are meaningful to patients. Please consider this during your discussion of FDA questions later on.

The next part of the presentation focuses on the safety results. The product was well tolerated, and the overall safety profile was very similar between the two treatment groups. As expected, since patients had target knee OA, events were observed from the joint. It is noteworthy that the incidence of target knee AE was almost identical between the two groups. Treatment with Synvisc did, therefore, not seem to impact the course of the disease in any negative way. There were no serious adverse events in the target knee in any of the two groups.

A few adverse events were assessed as

related to the device, and the incidence was similar in the two treatment groups. In the target knee, device-related events were arthralgia, effusion, arthritis, arthropathy, and injection side pain. All of these had a short duration and were treated symptomatically. Outside the target knee, there was also a similar incidence in the two groups, and there were few serious adverse events overall. There were five patients in the Synvisc arm having serious adverse events. They were angina, ingrown hernia, bradycardia, cervical hernia, and noncardiac chest pain. There were three patients in the control arm who experienced serious events. They were a femur fracture, radial nerve palsy, and transitional cell carcinoma of the urethra.

The incidence of related events outside the target knee was even lower and they were related to the injection. There was one patient who fainted in the Synvisc arm and one patient in the control arm who experience nausea or bone pain. And there were no patient deaths.

Most of the adverse events were a mild to moderate intensity. There were few events that were of a severe intensity, and importantly, none of them were related to the device. There were seven

patients in the Synvisc-One arm who experienced events of this intensity. In five patients, no treatment was required, and two patients got oral medication for arthralgia. None of the patients discontinued due to an adverse event, and importantly, no patients experienced severe acute local inflammatory reactions.

What we were interested to investigate was if repeat treatment constituted an additional risk. In this table is shown the number of patients with any device-related target knee OA, as assessed by the investigator. There were four patients experiencing five different events listed here. They were arthralgia in two patients, injection side pain in one patient, arthritis in one, which was a return of osteoarthritis pain symptoms, and one patient experienced an injection side hematoma.

These events are similar, in terms of character and incidence, as what we observed in the initial phase. We did, therefore, not identify any new safety signal, and repeat treatment therefore seems to be safe.

So, to summarize, the safety profile in this study was overall very benign. With the exception of three events that were related to the

injection itself, there were no device-related systemic adverse effects. Injection of six milliliters of Synvisc-One resulted in a similar safety profile as arthrocentesis and injection of saline.

No new safety signals were observed with a single injection of a larger volume of Synvisc, and repeat treatment with six mL's of Synvisc-One did not change the safety profile. I would, therefore, like to conclude that this study gives valid scientific evidence providing reasonable assurance of effectiveness.

And I would like now to hand over the podium to Dr. Elkins, who will present the underlying statistical methodology in more detail. Dr. Elkins is the Director of Biostatistics at Genzyme.

MS. ELKINS: Good morning, Panel members, ladies and gentlemen. Later today, the FDA will be asking you some questions related to statistical considerations. I want to take this opportunity to walk you through some of the statistical aspects of the pivotal trial to aid you in responding to these questions.

One of the FDA's statistical questions is related to the analysis method for efficacy

endpoints. I would also address the need to control the Type I error or, as it is otherwise known, multiplicity, and the power of the study to detect the statistically significant difference between treatment groups for the primary efficacy endpoint.

Firstly, I will address the efficacy analysis methods. The pre-specified analyses Genzyme performed, as you have just seen in Dr. Holmdahl's presentation, resulted in statistically significant differences between the Synvisc-One and control group, for the primary efficacy endpoint, WOMAC A, and the secondary efficacy endpoints, WOMAC A1, PTGA and COGA. The analyses the FDA presented in their briefing document resulted in a statistically significant difference for the WOMAC A and WOMAC A1, but with different results for the PTGA and COGA.

This slide presents a timeline of statistically related activities for the pivotal study. As you can see, the statistical analysis plan was finalized prior to database log, and the treatment assignments were not made available to the statistical group until after database log. The analyses were then performed by a contract research organization, according to the pre-specified statistical analysis plan. Genzyme has presented

these analyses today. The FDA then conducted, or asked Genzyme to conduct, various different analyses following submission of the sPMA. The FDA will present the final version of these analyses today.

I would like to take some time to explain the differences between Genzyme and FDA analysis methods. For the primary efficacy endpoint, the only differences between Genzyme's analysis and the FDA's final analysis was that Genzyme treated site as a fixed effect and analyzed the change from baseline, whereas FDA treated site as a random effect and analyzed the absolute value. Using change from baseline or the absolute value of a variable makes no difference to the estimated treatment effect and its associated p-value since the baseline is included as a covariant in the model. Fixed versus random effect is the preference in designing multicenter clinical trials. However, as you can see from this slide, this difference did not change the interpretation of the WOMAC A results. The p-value changed from 0.047 using Genzyme's analysis to 0.32 using FDA's final analysis.

There were more substantial differences between Genzyme and FDA's analysis of ordinal secondary endpoints. The secondary endpoints, WOMAC

A1, PTGA and COGA, are ordinal data. Here you can see a screenshot of Genzyme collected WOMAC A1 for this study. The patient had to choose one of these ordered categories. They couldn't choose halfway between moderate and severe, for example. This means that ordinal scales, such at the Likert, are very different to a visual analog scale, where the patient is asked to mark their pain anywhere along a line from no pain to extreme pain.

We originally proposed a visual analog scale for this study and proposed a similar analysis to the FDA's. However, we decided that because of the practical reasons of conducting a study with electronic data capture, the patient-reported outcomes should be captured using the Likert scale. Therefore, the model you see on the left was pre-specified in the statistical analysis plan, and the results of this analysis are presented today. The FDA analyzed these ordinal endpoints using the repeated measures analysis of covariance. We chose the GEE proportional odds, as it accounts for the ordinal nature of the data, the ordered categories, whereas the analysis the FDA was using treats these ordered categories as if they are continuous data.

This slide presents why the proportional

odds model is an appropriate way to analyze ordinal data. It should be noted that analysis of covariance may be a robust analysis, but the proportional odds models have been developed specifically for this type of data and are commonly used to analyze ordinal data from a Likert scale.

Because the WOMAC A is the mean of five items, we can assume these are continuous data and use methods designed for continuous data. It is therefore appropriate to analyze the WOMAC A using repeated measures, ANCOVA. For the WOMAC A1, PTGA and COGA, which are a single ordinal response, it is more appropriate to use statistical methods designed for this type of ordinal data. The assumptions required for the proportional odds model, for these ordinal endpoints, was formally tested using score tests. The p-values were not significant for these tests, as shown at the bottom of this slide. This means that the proportional odds assumption was met for all three of these ordinal endpoints. Because of this, Genzyme is confident that this is the most appropriate way to analyze the data, as we pre-specified in our statistical analysis plan.

This slide is intended to show the history of re-analyses conducted by FDA. All FDA re-analyses

confirm the result presented by Genzyme for the primary efficacy endpoints. Some of the FDA re-analyses of the secondary endpoints were supportive of Genzyme's pre-specified analyses, whilst others were not. The data in the first column is the analysis Genzyme pre-specified and presented today.

Analysis 2 is the analysis FDA has requested for other similar viscosupplement IDE studies conducted by Genzyme, which have been mentioned in earlier presentations today. The details of these and other FDA analyses were provided to you in your Panel pack.

Analyses 5 and 6 are the analyses FDA has presented in their briefing document as their final analyses. It should be noted that for FDA Analysis 6, there is a very large loss of power. This is due to FDA making these endpoints into binary endpoints when they were in fact collected using five categories; that is, for example, for the WOMAC A, there were categories none, mild, moderate, severe, and extreme. These were reduced to two categories, none and mild versus moderate, severe, and extreme. This analysis is also a landmark analysis at week 26, whereas the other analyses presented in this table include all post-baseline data.

So, in conclusion, all FDA re-analyses confirmed the statistically significant results presented by Genzyme for the primary efficacy endpoint. Some of the re-analyses of the secondary endpoints were supportive of Genzyme, while others were not.

Another question the FDA had that Genzyme would like to address is the requirement to adjust secondary endpoints for multiplicity. The pivotal study being discussed today was conducted with reference to ICH E9 statistical principles for clinical trials. This is industry standard and accepted by regulatory agencies.

ICH states that multiplicity may arise for the following reasons: from multiple primary variables, multiple comparisons of treatment for the primary endpoint, repeated evaluations over time for the primary endpoint, and interim analyses. The only area in our study for which we therefore need to address multiplicity was the repeated evaluations over time for the primary efficacy endpoint. As recommended in ICH E9, we did this by using repeated measures analysis.

In our response to the FDA's deficiency letter, we did propose a hierarchical sequential

testing ordered method. However, we did this at FDA's request, but we did not feel it was necessary to perform any adjustments.

So, in summary, for the primary efficacy endpoint, we used repeated measures analysis; therefore, no adjustment is necessary. For secondary efficacy endpoints, the purpose of secondary efficacy analysis is to show consistency. Since these are considered supportive of the primary efficacy endpoint, and we are not asking for additional -- indication based on these endpoints, there is no requirement to adjust the multiplicity.

We are fortunate to have Professor D'Agostino with us today who has published on this topic. He will be happy to answer any questions the Panel may have on this issue.

Finally, I would like to talk about the power of the study to detect the statistically significant difference between the treatment groups for the primary efficacy endpoint. The sample size determined for this study was based on 80 percent power and a Type I error of five percent, using assumptions from an open-label study of Synvisc. Power and sample size calculations are performed during the design phase of a study using estimates.

We used 0.297 as an estimate of the treatment effect for sample-size calculations only, not as a criteria for success of the study.

The success of the study was defined in the protocol as a statistically significant difference between the treatment groups in the primary efficacy endpoint. Also, it should be noted that 0.297 is included in the 95-percent confidence interval for the primary efficacy endpoint observed for this study. A retrospective power calculation attempts to determine the power of a study after data has been collected and analyzed, and is not relevant to the interpretation of the results.

We believe our study was powered correctly, using the information we had at the time of the study design, and therefore we were able to detect the statistically significant difference in our primary efficacy endpoint.

So, in conclusion, the Synvisc-One pivotal trial met its pre-specified primary efficacy endpoint. Five FDA re-analyses confirmed the significance of this primary endpoint. Multiple FDA post hoc analyses of the secondary endpoints showed variable statistical significance using different methodologies.

While there are several concerns about duplicability of these methodologies for this data, these results did not change the fundamental conclusion of either the primary endpoint or the supportive results of the secondary endpoints. We also believe multiplicity is not an issue for this study and that this study was powered correctly.

I now want to introduce Dr. Robert Dworkin who is a professor at the University of Rochester School of Medicine and Dentistry. Dr. Dworkin is a recognized expert on chronic pain outcome measures in clinical trials. He will be speaking to you today regarding how to define and interpret clinical significance, in clinical trials, with pain.

DR. DWORKIN: Thanks very much, Clare. Good morning. I'm Bob Dworkin from the University of Rochester, and I'd like to start off by disclosing, as it says at the bottom of this slide, that I'm receiving consulting fees and reimbursement for my travel expenses from Genzyme Biosurgery. And as you can see from this slide, Genzyme has asked me to give a brief presentation on the determination of clinical meaningfulness in randomized clinical trials of chronic pain treatments. And so by way of introduction, just to tell you a little bit about who

I am, my research consists of really two areas. I do clinical trials of treatments for both acute and chronic pain, and in addition, I'm intensely interested in and conducted studies of methodologic aspects of clinical trials of treatments for acute and chronic pain.

I'm a former consultant to and member of the Anesthetic and Life Support Drugs Advisory Committee at CDER, currently a member of the OARSI-FDA Osteoarthritis Claim of Symptomatic Relief Working Group, and most importantly for today's presentation, I've co-chaired, since 2000, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.

The acronym is IMMPACT. And what IMMPACT is, as the slide indicates, it's a consortium with representatives from academia, regulatory agencies, both the FDA and EMEA, government agencies like NIH and the VA, patient advocacy groups, and pharmaceutical and device industry. And you'll hear quite a bit more about IMMPACT in a moment. The objectives of my brief talk this morning are really to address FDA Question 1 in the briefing materials, and that specifically is whether the .15 difference between treatment groups in the pivotal Synvisc-One

clinical trial is clinically meaningful.

And so what I'm going to do is spend a little bit of time discussing the clinical meaningfulness of patient improvements in chronic pain trials, then talk about the clinical meaningfulness of group differences in chronic pain trials, and then emphasizing the critical difference between these, determining patient improvements and whether they're clinically meaningful versus group differences. I'll end up by discussing approaches for determining the clinical meaningfulness of group differences.

So I mentioned IMMPACT a moment ago, and this is one of the earlier IMMPACT publications. As you can see, there are lots of authors representing the diverse and numerous stakeholders. And in this article what we did -- this was actually the second IMMPACT article -- we made recommendations for what would be considered, what could be considered core outcome measures to be used in chronic pain clinical trials. And after publishing this in 2005, the question very quickly came up, given that IMMPACT has recommended a set of core outcome measures, what would be clinically important improvements to patients in that set of outcome measures? And so

this is relatively recent IMMPACT publication that followed up on that earlier one, so you can see, earlier this year, we talked about how to interpret the clinical importance of treatment outcomes in chronic pain trials.

And I should just mention at this point that this long list of authors includes a number of people from CDER, Laurie Burke, who you'll hear more about in a few minutes, Bob Rappaport, Sharon Hertz. Jim Witter is on there. Currently, Dr. Ann Costello from CDRH has become involved in IMMPACT and has attended the last three meetings. We're a little bit behind in publications.

So what did we do in this article? What we said is, is that we've listed -- we've recommended a number of outcome measures for use in pain clinical trials. You can't see this here. And then, for each of these measures, we recommended what would be clinically meaningful changes, and I've highlighted the measure that's most relevant for today's meeting, which is a 0 to 10 pain intensity scale, where 0 is no pain and 10 is the worst possible pain you can imagine. And what we said in this publication earlier this year is that on that 0 to 10 scale, using that 0 to 10 scale as an outcome measure, a

reduction over the course of a trial, from baseline to endpoint, of 10 to 20 percent is what a patient would consider a minimal clinically meaningful improvement, whereas reduction of 30 percent or greater is a more moderately clinically meaningful improvement. And finally, a reduction by half, 50 percent or greater, from baseline to endpoint, patients consider a substantial clinically meaningful improvement, a home run, if you will.

Now, how did we come up with those recommendations for reductions in pain over the course of chronic pain clinical trials? Well, primarily we looked at the literature, using anchor-based determination of what clinical -- of what patients considered clinically meaningful improvement. And so here's an example of an anchor that's used in such studies. At the end of the trial, the patient rates, in their view, what has been their overall status as a function of treatment in the trial.

So here, as you can see from this patient global impression of change scale, patients rate at the end of the trial, are they very much improved, do they think they're much improved, do they think they're minimally improved, so on and so forth. And

the pivotal publication that we paid attention to, in coming up with our IMMPACT recommendations, was this very widely cited, very influential article by John Farrar and colleagues that looked at the relationship between reduction in pain and patient ratings of overall improvement across a large number of clinical trials in neuropathic pain conditions, like painful diabetic neuropathy, postherpetic neuralgia, in nonneuropathic musculoskeletal conditions, like osteoarthritis and chronic low back pain, in fibromyalgia and so on.

And across all of these trials, in this kind of meta-analysis, what John and his colleagues showed is this very tight linkage between the reduction in pain over the course of chronic pain clinical trials, whether it was in the active treatment arm -- and these are all pregabalin trials -- or the placebo arm, a very tight linkage between what patients reported as their reduction in pain and what they considered minimal, moderate and substantial improvements.

And from this figure, and others like it in the article, we were able to then recommend that a 10 to 20-percent reduction is a minimally important improvement in the patient's perspective, and that a

greater than 30-percent reduction was a moderately important improvement to patients, whereas a reduction by half or more is a substantial improvement.

Okay. What we then did in this article is to say that we have focused on the determination of what patients themselves consider clinically meaningfully important. But how can we interpret group differences and their clinical importance? And what we said -- and in fact, the article is not about the interpretation of what's a clinically important group difference because we said it is crucial to recognize that criteria for clinically important change in individuals cannot be directly applied to the evaluation of clinically important group differences.

We then went on to say, for example, in evaluating a new analgesic, if a two-point decrease on a 0 to 10 numerical rating scale of pain intensity is considered a clinically important improvement for an individual patient, it should not be inferred that a two-point difference in pain reduction between the analgesic and placebo must occur before the treatment benefit can be considered clinically important.

So we were very careful to distinguish our

recommendations about what patients consider a clinically meaningful benefit, from how one might then go about determining whether the group difference between treatment arms is clinically meaningful.

Now, in tandem to our IMMPACT effort, the FDA was preparing this draft guidance on patient-reported outcome measures and their use in medical product development to support labeling claims. This draft guidance, which is available on the web and I guess elsewhere, has been prepared by the study endpoint and label development group at the FDA, and as you can see from the bottom of this slide, this has involved individuals from CDER, from CBER and from CDRH. And, in fact, when I said that this was prepared in tandem to the IMMPACT recommendations, Laurie Burke was pivotally involved in both the IMMPACT process and the development of this draft guidance.

And what this draft guidance has to say about this topic is somewhat similar to what IMMPACT said. The FDA draft guidance says, for many widely used measures, pain, treadmill distance, and the Hamilton depression rating scale, the ability to show any difference between treatment groups has been

considered evidence of a relevant treatment effect.

They go on to say, when defining a meaningful change on an individual patient basis, for example, a responder index, that definition is generally larger than the minimum important difference for application to group mean comparisons. Now, this is an important point, that what patients consider a meaningful benefit is generally larger than group differences that can be considered meaningful, as illustrated, I think, really wonderfully well on this slide. This is from meta-analysis of clinical trials of very different types of treatments for knee osteoarthritis pain.

And what these investigators did is to plot, on the same graph, thresholds of what patients consider clinically meaningful benefits. This is 10 millimeters on a 0 to 100 millimeter visual analog scale. And these authors said that 10 millimeters -- and this is similar to IMMPACT -- can be considered the minimal clinically meaningful benefit to a patient.

But what they then put on the same graph are the treatment differences between active treatment and placebo in clinical trials of a diverse range of treatments for osteoarthritis knee pain.

And as you maybe can see from the right-hand side of the slide, oral NSAIDs, topical NSAIDs, intra-articular steroids, paracetamol, which of course is Tylenol, so on and so forth.

And you can see, in every case, the difference between these active treatments and placebo in these clinical trials -- and there are about 200 in this study, as I recall -- at week six, week eight and week 12, with less than this minimal perceptible difference that the authors argued patients consider a minimal clinically significant benefit, except for this curve here, which is opioid analgesics. And I won't say more about opioids because I can say too much about opioids if I got started.

All right. So this previous figure illustrated that the improvement that patients with osteoarthritis considered clinically meaningful is larger, just like the FDA draft guidance said, than the differences found between active treatment and control groups in osteoarthritis knee pain clinical trials.

Why is this so? Well, one reason I think that explains a lot of it is that meaningful change in individual patients reflects treatment effects, of

course, but it also reflect placebo and other nonspecific effects of the clinical setting. It reflects natural history and spontaneous resolution, and it reflects statistical regression to the mean, whereas group differences between an active treatment and the control groups simply reflect the incremental benefit associated with the active treatment that contributes to improvement. So there's a kind of apples and oranges here in terms of what accounts for clinically meaningful change in an individual patient versus clinically meaningful, or not, differences between groups in a clinical trial.

Now, this is illustrated in data that you've already seen, the Synvisc-One pivotal trial, where, on average in the Synvisc-One arm, patients decreased in pain about 36 percent, which by IMMPACT criteria and everybody else's criteria, in an individual patient would be a moderate to substantial clinically meaningful improvement, a 36-percent reduction over the course of the trial. And this is a 26-week trial, whereas the patients in the control arm also improved, not surprisingly, as you'll see in a moment, but that that improvement was less in the control arm. And Dr. Holmdahl, of course, talked about this in detail.

Now, the other factor, I think, that accounts for these different magnitudes between the extent to which patients improve and the differences between treatment arms in a clinical trial is that the differences between active treatment and control groups are limited by the magnitude of placebo effects in chronic pain clinical trials, and we know that these can be substantial. And they're also limited by the use of rescue and concomitant analgesics, which have to be used in trials that include a placebo group. It would be unethical not to include rescue and concomitant analgesics in a placebo control trial. So the use of these rescue and concomitant analgesics, and the substantial placebo effect in clinical trials, also attenuates the magnitude of the difference that can be found between active treatment and the control group. And the placebo effects in osteoarthritis trials were recently examined in this meta-analysis, and what I've highlighted here on this slide is that the placebo effects -- this is really the response in the placebo arm, which includes placebo effects and other factors -- were greatest in this meta-analysis in clinical trials of acupuncture and intra-articular hyaluronic acid.

And, in fact, the authors did a multi-varied analysis, multi-regression, where they showed that the three factors that were most potent in predicting magnitude of the response in placebo groups in osteoarthritis trials were the magnitude of the treatment effect, the effect in the treatment arm, and the severity of the baseline pain, and finally, the invasiveness of the treatment intervention.

When the treatment intervention was more invasive, like acupuncture, injection, or surgery, the response in the placebo arm was greater. And that's consistent with this breakdown, highlight acupuncture and intra-articular hyaluronic acid. So let me begin to wrap up in the next two or three slides.

So evaluations. I tried to argue that evaluations of the clinical meaningfulness of group differences between chronic pain, active treatment in control groups in chronic pain clinical trials, should not be based on criteria for evaluating clinically meaningful changes within individual patients. Rather, I think, they should be based on case-by-case considerations of various characteristics of the specific treatments.

And what are these characteristics? Well, this is a long and busy slide. These are my lists of factors that I think should be considered to determine in establishing the clinical meaningfulness of group differences. And I start off by saying that what's necessary, but not sufficient, is the statistical significance of the primary efficacy analysis, and that's why I put the little check mark there. If you don't have this, there's no reason to then go down the list.

But if there is statistical significance in the primary efficacy analysis, to then, the next step, I think, to interpret the clinical meaningfulness of the group difference, one would like, would want to consider, one really needs to consider results for secondary endpoints, results of responder analyses, the magnitude of the improvement with treatment, the rapidity of the onset and the durability over time of treatment benefits, the plausibility of the treatment benefit, safety and tolerability, of course, the treatment effect size compared to whatever else is available for the condition, limitations of available treatments, the different mechanism of action of the treatment, if it's a different mechanism of action compared to

existing treatments, the convenience of the treatment and the likelihood of patient adherence with the treatment -- and then, as you see, I ran out of room here -- other benefits, including improvements in physical and/or emotional functioning, whether there are drug interactions or not, and the cost of the treatment.

So my conclusion -- and this is my last slide -- is that the clinical meaningfulness of patient improvements in chronic pain trials can be determined -- and I think this is a fairly straightforward process -- by assessing what patients themselves consider meaningful improvement, whereas the clinical meaningfulness of group differences in chronic pain trials must be determined by a multi-factorial evaluation, a multi-factorial consideration of the benefits and risks of the treatment in light of other available treatments for the condition. Thank you very much for your attention.

It's my great pleasure to introduce the next speaker, Dr. Lee Simon, who's Associate Clinical Professor of Medicine at Harvard Medical School and at Beth Israel Deaconess Medical Center.

DR. SIMON: Thank you, Dr. Dworkin. Panel members, Mr. Chairman, ladies and gentlemen, I'm

Lee Simon, and I'm here to give a review of what is maybe most important, the clinical implications of the study results that you've just now been exposed to. Prior to beginning, I'd first like to say, as with Dr. Dworkin, I am here at the behest of Genzyme Biosurgery, and I'm receiving compensation for my time as well as compensation for and reimbursement for my travel expenses.

In introduction to this committee, I'd just like to make a comment or two, that I've been a clinical rheumatologist for 25 years, I serve on the executive committee of OMERACT, which is Outcome Measures in Rheumatic Disease Clinical Trials. This is an international group that's loosely affiliated with the World Health Organization and has led to recommendations that have been commonly adopted by regulatory agencies around the world for measurement of clinically important outcomes in clinical studies and subsequent approval of various different therapies.

Furthermore, I'm co-chair of the Osteoarthritis Research Society International Committee to address request for proposal from the FDA on updating the Draft Osteoarthritis Guidance of 1999. Dr. Dworkin has already mentioned this, and he

sits on one of the working committees. And I am former Division Director of Analgesic, Anti-Inflammatory and Ophthalmological Drug Products within CDER of the FDA.

I'd like to point out several things about the key results for Synvisc-One that I think are very important. First, that the primary endpoint analysis for the WOMAC A, the pre-specified primary endpoint, which is pain, over 26 weeks demonstrated statistical superiority, as you've heard, of p-value equal to 0.047.

I'd also like to point out that the control arm is not actually placebo, as you've heard over and over again. It's actually a therapeutic arm, where you stick a needle in, you take out fluid if it's there. Certainly, we all know as clinicians that makes people feel better. Furthermore, inducing or putting in intra-articular saline can actually lead to improvement as well. Orthopedic surgeons have used lavage for years, although it's debated on its utility.

Secondly, I'd like to point out that, as you've mentioned -- as has been mentioned by Dr. Dworkin, clearly, secondary outcomes are supportive of primary events, and the Synvisc-One

study demonstrated statistically superior secondary outcomes to control, and that includes WOMAC A1, pain on walking, patient global assessment, a critical component of determining clinical meaningfulness, and the clinical observer global assessment that was consistent with what the patient felt on their results.

Now, I'd like to point out two other issues. The first is you've heard these numbers before, but I'd like to talk about them for a minute. Patients who received Synvisc-One showed a significant decrease in pain, from baseline, of approximately 35.8 percent over 28 weeks, which was a statistically significant change.

It was also significantly better even though the control group also showed statistical significant improvement. So, therefore, there was great rigor here because the drug itself was better than the control group, where both were better than baseline. This is consistent with the literature on clinically important improvements in osteoarthritis patients who are treated with various different therapies, and that includes those that have been approved for pharmaceutical and medical device products for the treatment of OA pain.

In addition, we learned that the observed treatment effect was amplified in a subset of patients who did not have osteoarthritis in the nontarget lower extremity. This is also a very big problem in analyzing outcomes in local therapy, and they, in fact, demonstrated significant benefit there.

In thinking about -- and as I've mentioned, this was in the same context as other results that we've seen before, let's review here approval of other local OA pain treatments. Hyalgan was approved on a VAS pain scale of a 50-foot walk test, with a six millimeter separation from saline. It's interesting to note that a topical nonsteroidal was recently approved.

With statistical superiority to vehicle alone, on walking pain on VAS scale, that difference was 7 millimeters at 12 weeks. But to actually accomplish this, the investigators had to exclude patients with pain in the contralateral knee. In this Synvisc-One study, that was not necessary to still achieve benefit. Furthermore, they had to exclude patients whose pain spontaneously declined between screening and treatment. Other viscosupplements I'll mention in a moment include

Supartz, Orthovisc, and Euflexxa. And they have been approved by various criteria. The level of evidence, therefore, provided for Synvisc-One was commensurate with these already approved products.

In looking at this more complicated slide, in the left-hand column you see systemic therapy, local therapy, such a diclofenac topical agent, local effect of three different hyaluronic acid supplements, and the local effect of Synvisc-One. Here are the references for this, these are the products in this column, and here are the percentages of responsiveness.

I've already referred to the 35.8 percent that you saw with Synvisc-One, and you'll appreciate the fact that even with systemic therapy, this is well within the range of what we've observed with systemic therapy, certainly within the range that we see with a topical nonsteroidal, certainly within the same effect range that we see with other viscosupplementation, and therefore it is meaningful.

Another way to express this evidence is to compare the effect size, as mentioned for Synvisc-One of 0.23, compared to three different systemic therapies, all of which are considered standard of care in the treatment of the appropriate patient with

osteoarthritis. And you can appreciate that the 0.23 is certainly within the range seen with acetaminophen, nonselective nonsteroidals, or COX-2 selective inhibitors.

So let me just say that as a clinician with significant experience in interpreting evidence in clinical trials, we see some very interesting positive risk benefit profile here. No serious adverse events have been reported. No new safety signals were observed. The types of adverse events that we observed were not different from that reported with the previously approved three-injection dosing of Synvisc.

There is no increase in incident local adverse events with repeated one-injection dosing. The clinical benefit was consistent in multiple outcome measures in secondary outcomes. And clearly, as you've heard from the open public forum, this could lead to increased convenience and, very importantly nowadays, increased adherence to therapy by having only one injection.

I'd like to conclude with this particular slide and remind the Committee that we have no cure for osteoarthritis, and it is clear, as a clinician, we need multiple choices. Viscosupplements give

similar treatment effect as observed with systemic therapies, such as that with nonselective nonsteroidals and COX-2 inhibitors, as well as those observed with local therapies.

Now, local therapies avoid potential GI, cardiovascular, and renal toxicity as represented by nonsteroidal anti-inflammatory drugs and acetaminophen. There is clearly, with this therapy, a reduced need for chronic oral therapy, a needed option for osteoarthritis patients who have failed oral meds, who have risks factors for those oral meds, who, in fact, are not candidates for actual surgical procedures or knee arthroplasty.

So I'd like to conclude with the idea that, in fact, we have seen evidence that there's clinically meaningful and statistically significant improvement from baseline in the a priori defined primary outcome. There is a clear, defined, acceptable risk benefit. And finally, as we've heard, that the pros of changing to an injection schedule may actually have advantages for patients and their providers. I thank you very much, and I'd like to call back Mike Halpin for conclusions.

MR. HALPIN: I'd like to very briefly summarize what you've reviewed today. Dr. Polisson

pointed out that OA is a significant medical need and that new options are needed. Local therapies have clear advantages over systemic therapies and their attendant toxicities.

Dr. Holmdahl reviewed the clinical effectiveness for Synvisc-One, and both the FDA and Genzyme agreed that the primary endpoint was met with a treatment effect of 0.15 and effect size of .23. The primary question today is what is the clinical meaning of this finding, and I'd just like to highlight three key statistically significant supportive analyses.

First, within patient improvement on WOMAC A and the primary endpoint from baseline was 0.82 on the Likert scale or a 36-percent improvement in pain; (2) WOMAC A1, pain on walking on a flat surface, had an effect size of 0.36. I'd like to point out this was an entry criteria into the clinical study and is a measurement tool that's frequently used for clinical trials of patients with moderate to mild osteoarthritis; (3) when you look at patients who only had symptomatic OA in the treated joint, you see an effect size of 0.44, which is even larger on WOMAC A.

Dr. Dworkin pointed out that when you're

looking at pain trials, it's important to look at within patient improvement as well as between group differences. And I'd just like to point out that if you look at that from that perspective, you see a 36-percent improvement in patients on the primary endpoint with Synvisc-One.

If you look at safety, Synvisc-One is the same material as Synvisc, with a 16-year history in over four and a half million patients. There are no new safety signals identified in the Synvisc-One trials, and 10,000 patients have been treated with Synvisc-One outside the U.S. for a spontaneous-reported adverse event rate of 0.14 percent, and no serious related adverse events have been reported. From a statistical point of view, the pre-specified analysis plan was appropriate and the multiple secondary endpoints support the clinical benefit.

In conclusion, the totality of the evidence demonstrates that the Synvisc-One clinical trial results represent a clinically meaningful treatment option for patients suffering from osteoarthritis and knee pain. At this time I'd like to conclude the Sponsor presentation, and the Sponsor is available for questions.

DR. MABREY: I'd like to thank the Sponsor

for an excellent presentation. At this point, does anyone on the Panel have a brief clarifying question for the Sponsor? I'll remind you that we have much more time later on in the day for deeper questions. But any specific questions? I'll go around with Dr. Evans. Any specific questions at this time?

DR. EVANS: I guess not at this time.

DR. MABREY: Okay. Dr. Goodman?

DR. GOODMAN: None.

DR. MABREY: Okay. Dr. Olsen?

DR. OLSEN: I don't have any.

DR. MABREY: Thank you. Dr. Skinner?

DR. SKINNER: None.

DR. MABREY: Thank you. Dr. Blumenstein?

DR. BLUMENSTEIN: One of the things that I didn't see, and I'm a little surprised, is an indication of how much missing data there were in the analyses, and what the pattern of those missing data are, whether they were considered to be at random or not, whether they were influenced by adverse events or not, and so forth. And this has to do with whether the p-value is true and significant.

MR. HALPIN: I'd like to have Clare Elkins come up and answer that question.

MS. ELKINS: The dropout rate in the study

was actually quite small. There was only seven percent of patients in the Synvisc-One group who dropped out, nine percent of the control group. We did a confirmatory analysis -- observation carried forward. Okay, slide. Slide on, please. And as you can see from this, there was very little impact on the -- observation carried forward, probably due to the low amount of dropout. Does that answer your question?

DR. BLUMENSTEIN: I still don't have a sense of how much missing data, how many missing visits. Did they tend to be concentrated at the end of the trial rather than at the beginning and so forth? I have no sense of missingness of quantity or whatever.

MS. ELKINS: Could we prepare a response and get back to you later about that?

DR. MABREY: Yes, why don't we work on that over lunch and get back to that. Thank you, Dr. Blumenstein. Ms. Rue, any questions?

MS. RUE: I don't have any questions right now.

DR. MABREY: Okay. Ms. George?

MS. GEORGE: No, I don't.

DR. MABREY: Okay. At this point, I'd like

to call a short 10-minute break. Panel members, please remember that there should be no discussion during the break, amongst yourselves or with any member of the audience. And we will resume at, let's just say, 10:15.

(Off the record at 10:05 a.m.)

(On the record at 10:15 a.m.)

DR. MABREY: It's now 10:15. I'd like to call this meeting back to order. The FDA will now give their presentation on this issue. Dr. Lee, you have 60 minutes.

DR. LEE: Chairman and the Panel members, thanks for reviewing this PMA. My name is Kevin Lee. I will present nonclinical and clinical presentation. Dr. Lao will present statistical issues, and Dr. Wang will present post-approval study.

Summary of non-clinical studies. Indications for use. Synvisc-One is indicated for treatment of pain in the osteoarthritis of knee in patients who have failed to respond adequately to conservation nonpharmacologic therapy and simple analgesics, e.g., acetaminophen. Synvisc was also approved for a total of three injections for the treatment of osteoarthritis in the knee, in 1997, by FDA. This present application is a change of

an alternative regimen.

Rationale for Panel meeting. Single dose regimen for intra-articular injection of hyaluronic acid is based on viscosupplementation. FDA is presenting Synvisc-One to the Panel primarily to comment on the clinical effectiveness of the device in relieving pain in patients who have OA of the knee. Panel questions will be presented.

Device Description. The device description is the same as the applicant described previously.

Pre-clinical testing. An evaluation of pre-clinical test by FDA is based in large part on the previous device approval, and FDA has not unresolved safety issues.

Clinical study summary. The clinical trial included initial phase and repeat treatment phase studies.

Pivotal study design. The primary study was conducted to evaluate the safety and efficacy of a single six milliliter intra-articular dose of Synvisc-One injected into the knee for a 26-week period from the baseline. The study was conducted as a randomized, double-blind, placebo-controlled, concurrent, and multicenter study.

The study was conducted at 21 sites in six

European countries. The study was not conducted in U.S., and nor was the study conducted under an investigational device exemption. Consequently, the FDA did not review the protocol prior to conduct of the study under an IDE. In this study, 253 patients were randomized, with a ratio one to one.

Group 1. Arthrocentesis is followed by a single six-milliliter intra-articular injection of Synvisc-One on day zero.

Group 2. Arthrocentesis followed by a single six-milliliter intra-articular injection of phosphate buffered saline placebo on day zero. The evaluator and the patient were blinded to the treatment group assignment.

Follow-up phase. All patients were scheduled to return for follow-up within specified visit windows at day zero (baseline), 1, 4, 8, 12, 18 and 26 weeks following the single injection. For 48 hours prior to each visit, patients were to forego pain or their OA medications that were otherwise permitted during the study.

Key inclusion and exclusion criteria described by applicant.

Primary efficacy objective. The primary efficacy objective was to demonstrate that a single

six-milliliter intra-articular injection of Synvisc-One provides superior pain relief over 26 weeks, as compared to a single six-milliliter intra-articular injection of a placebo in treating patients with symptomatic primary OA of the knee using the WOMAC A scale. WOMAC A for pain score, that is the primary endpoint included by Likert scale, Likert grades in each of the five pain questions and was described by the applicant.

Rescue medications. Patients were allowed to take rescues medications for the target knee pain relief throughout duration of the trial, including during the screening phase, with the exception of within 48 hours prior to study evaluations. Other permitted pain medications are listed in the protocol.

As to the demographic characteristics, the two groups were comparable to each other in age, sex, and weight.

Safety. Safety was determined using the incidence of treatment-emergent adverse events vital signs and physical examination findings. Adverse events were categorized using standardized coding dictionary.

Adverse events. Adverse events were