U.S. Food and Drug Administration

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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE

WEDNESDAY, SEPTEMBER 16, 2009

8:30 a.m. to 3:00 p.m.

Holiday Inn Gaithersburg

Two Montgomery Village Avenue

Gaithersburg, Maryland

Diane Aronson (Consumer Representative)
Consumer Advocacy
P.O. Box 410305
Cambridge, MA 02141

Lenore Buckley, M.D., M.P.H.
Professor of Internal Medicine and Pediatrics
Virginia Commonwealth University
School of Medicine
P.O. Box 980102
Richmond, VA 23298

Nancy Olsen, M.D.
Professor of Internal Medicine
McGee Foundation Chair in Arthritis Research
University of Texas Southwestern Medical School
5323 Harry Hines Boulevard
Dallas, TX 75390

Kathleen O'Neil, M.D. (Chair)
Associate Professor of Pediatrics
Department of Pediatrics
Division of Rheumatology
University of Oklahoma College of Medicine
940 N.E. 13th Street, Bielstein 3B3303
Oklahoma City, OK 73104

Kenneth Saag, M.D.
Associate Professor
Department of Medicine
Division of Clinical Immunology and Rheumatology
The University of Alabama at Birmingham
820 Faculty Office Tower
510 20th Street South
Birmingham, AL 35294

TEMPORARY VOTING MEMBERS

William Brackney (Patient Representative)
Henderson, NV 89011

Mustafa Haque, M.D.
Clinical Assistant Professor
Department of Orthopedic Surgery
Georgetown University Hospital
Hand Surgeon
Summit Orthopaedic Surgery
5530 Wisconsin Avenue, Suite 1660
Chevy Chase, MD 20815

Saul Kaplan, M.D.
Hand Surgeon
Mid-Atlantic Permanente Medical Group
6501 Loisdale Court
Springfield, VA 22150

Kathleen Mazor, Ed.D.
Associate Professor of Medicine
University of Massachusetts Medical School
630 Plantation Street
Worcester, MA 01605

Timothy McAlindon, M.D., M.P.H, M.R.C.P.
Professor of Medicine and Natalie V. Zucker and
Milton O. Zucker Chair of Rheumatology
Tufts University School of Medicine
Chief, Division of Rheumatology
Tufts Medical Center
35 Kneeland Street 4th Floor
Boston, MA 02111

William Swartz, M.D., F.A.C.S.
Clinical Associate Professor of Surgery
University of Pittsburgh, Department of Plastic
Surgery
Specialties of Plastic, Hand and Microsurgery, P.C.
5750 Centre Ave. Suite 180
Pittsburgh, PA 15206

Michael Weisman, M.D.
Division of Rheumatology
Department of Medicine
Cedars-Sinai Medical Center
8700 Beverly Boulevard
Los Angeles, CA 90048

FDA Non-Voting
Curtis Rosebraugh, M.D., M.P.H
Director, Office of Drug Evaluation II
CDER/FDA

Bob Rappaport, M.D.
Director, Division of Anesthesia, Analgesia and
Rheumatology Products
CDER/FDA

Sarah Okada, M.D.
Clinical Team Leader, Division of Anesthesia,
Analgesia and
Rheumatology Products
CDER/FDA

Eric Brodsky, M.D.
Clinical Reviewer, Division of Anesthesia, Analgesia and Rheumatology Products
CDER/FDA

Kathryn O'Connell, M.D., Ph.D.
Drug Risk Management Analyst
OSE/CDER/FDA

I N D E X

P R O C E E D I N G S

8:30 a.m.

DR. O'NEIL: Good morning. My name is Kathleen O'Neil, and I'm an associate professor of pediatrics and rheumatology at the University of Oklahoma in Oklahoma City. We are ready to begin the meeting of the FDA Arthritis Advisory Committee.

I would like to start by asking everyone at the table to introduce themselves, starting here with Dr. Haque.

DR. HAQUE: My name is Mustafa Haque. I'm a practicing orthopedic hand and upper extremities surgeon in Chevy Chase, Maryland.

DR. SWARTZ: Good morning. I'm Bill Swartz from Pittsburgh, Pennsylvania. I'm a practicing hand surgeon, been in practice for 30 years.

DR. S. KAPLAN: Saul Kaplan, Fairfax, Virginia. I'm an orthopedic hand surgeon in practice.

DR. MAZOR: Kathy Mazor. I'm associate professor at the University of Massachusetts Medical School. I'm not a physician. My background's in education, psychometrics, patient education and

physician-patient communication.

DR. McALINDON: I'm Tim McAlindon. I'm chief of rheumatology at Tufts Medical Center, and professor of medicine at Tufts University School of Medicine. I'm a clinical rheumatologist. I also do clinical investigations into rheumatic diseases.

DR. OLSEN: I'm Nancy Olsen. I'm a professor of medicine at the University of Texas Southwestern Medical School in Dallas. I'm a rheumatologist in academic practice, and I'm interested in autoimmune diseases.

DR. BUCKLEY: I'm Lenore Buckley. I'm a professor of medicine and pediatric at Virginia Commonwealth University, and I do both adult and pediatric rheumatology.

DR. VESELY: Nicole Vesely, designated federal official, Arthritis Advisory Committee.

DR. SAAG: Good morning. I'm Ken Saag. I'm a professor of medicine and epidemiology at the University of Alabama at Birmingham, where I direct the AHRQ-funded Center for Education and Research in Therapeutics.

MS. ARONSON: I'm Diane Aronson. I'm a consumer representative, standing member of the Arthritis Committee. I'm from Cambridge, Massachusetts.

MR. BRACKNEY: Bill Brackney. I'm from Henderson, Nevada, and I'm a patient representative.

DR. WEISMAN: I'm Michael Weisman, director of the Division of Rheumatology at Cedars-Sinai Medical Center, and professor of medicine at UCLA School of Medicine. And I'm a rheumatologist, interested in outcomes and risk for rheumatic diseases.

DR. O'CONNELL: Good morning. My name is Kathryn O'Connell. I'm a medical officer in FDA's Division of Risk Management.

DR. BRODSKY: Good morning. My name is Eric Brodsky. I'm a medical officer in rheumatology at the FDA.

DR. OKADA: Hi, Sarah Okada, clinical team leader of the Division of Anesthesia, Analgesia and Rheumatology Products, and I'm an adult rheumatologist.

DR. RAPPAPORT: Good morning. I'm Bob Rappaport. I'm the director of that division.

DR. ROSEBRAUGH: Curt Rosebraugh, director of the Office of Drug Evaluation II.

DR. VESELY: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting

with the media until its conclusion. Also, the Committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

And now for the conflict of interest statement. The Food and Drug Administration is convening today's meeting of the Arthritis Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the Committee 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 Committee's compliance with federal ethics and conflict of interest laws covered by but not limited to those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act is being provided to participants in today's meeting and to the public.

The FDA has determined that members and

temporary voting members of this Committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts, when it is determined that the agency's need for particular individual 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 federal employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of this Committee 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 USC Section 208, their employers.

These interests may include investments,

consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

Today's agenda involves discussion of collagenase clostridium histolyticum for the proposed treatment of advanced Dupuytren's disease under Biologics License Application 125338, sponsored by Auxilium Pharmaceuticals. This topic is a particular matter involving specific parties. Based on the agenda for today's meeting and all financial interests reported by the Committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing members and temporary voting members to disclose any public statements that they have made concerning the product at issue. We would like to remind members and temporary voting members that if the discussions involve any products or firm 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.

The FDA encourages all other participants to advise the Committee of any financial relationships that they may have with any firms at issue. We also just wanted to note that there is not an industry representative for this meeting.

Thank you.

DR. O'NEIL: Our first speaker this morning will be Dr. Bob Rappaport, the director of the Division of Anesthesia, Analgesia and Rheumatology Products at CDER FDA.

DR. RAPPAPORT: Thank you. Good morning, everybody. I don't think a lot of people in the public realize the time and effort and resources that the people who sit on our committees give us, give the FDA and the American public by participating. Our Committee members serve for periods from anywhere from two to four years, and during that time, they may cover numerous meetings and help us in other projects. And it's really -- as they're well-aware, they're paid a pittance for doing this. And we really do

appreciate their service.

So on behalf of the FDA, I'd like to take a brief moment to recognize one of our committee members whose term expires at the end of September.

Dr. Saag, would you come up?

Dr. Ken Saag has served on the Arthritis Advisory Committee since August of 2006. He's a professor in the Department of Medicine, Division of Clinical Immunology and Rheumatology at the University of Alabama at Birmingham. His expertise in rheumatoid arthritis and osteoporosis has brought a valuable knowledge base to this Committee's discussions, and his experience as both a clinician and researcher has proved invaluable.

So in appreciation of this service, the FDA would like to recognize Dr. Saag's service with this plaque.

Thank you very much.

DR. SAAG: Thank you very much, Bob.

DR. O'NEIL: Thank you, Dr. Rappaport.

We will begin the business portion of the meeting with some opening remarks from Dr. Sarah

Okada, who is the clinical team leader, also at the Division of Anesthesia, Analgesia and Rheumatology Products.

DR. OKADA: Good morning, everyone. I'd like to welcome you all and thank our Advisory Panel once again for taking time out of your busy schedules to join us for today's meeting. The topic for discussion today is Auxilium Pharmaceutical's clostridial collagenase, also known as AA4500 or Xiaflex, as a nonsurgical treatment of Dupuytren's contractures.

So in addition to our esteemed Arthritis Advisory Committee regulars, whose continued support we greatly appreciate, we have several special guests joining our panel today. Since the management of Dupuytren's disease has historically been the purview of our surgical colleagues, we're fortunate today to have several hand surgeons on the panel. So I'd like to extend a special thanks to Drs. Haque, Swartz and Kaplan for joining us today.

We're also fortunate to have two members of the Drug Safety and Risk Management Advisory

Committee, Dr. McAlindon and Dr. Mazor.

Today, we'll be starting off with the sponsor presentations, which will cover in depth the efficacy and safety data for AA4500, in addition to their proposed risk management activities. Then the main FDA presentation by Dr. Eric Brodsky will contain only a brief discussion of efficacy, which is not in question, and focus more on the safety data in the trials and concerns relative to generalizability of study results.

Following this, we will have a brief overview of risk management considerations in the FDA approval process by Dr. Kathryn O'Connell from the Office of Surveillance and Epidemiology.

Finally, we will be asking the Committee to discuss the proposed training for health care professionals in clinical practice, whether this training is adequate, and what factors will facilitate the assimilation of the training for the safe and effective use of this product, as well as to discuss the overall risk/benefit profile of the product and whether you recommend the product be approved.

Again, our deepest thanks to the panel, and we look forward to hearing your views. So without further adieu, I'll turn this back over to Dr. O'Neil.

DR. O'NEIL: Thank you. We will now move on to our presentation by Auxilium Pharmaceuticals, sponsors of this product. The first speaker who will introduce the product is Dr. Benjamin Del Tito, senior vice president, Quality and Regulatory Affairs, at Auxilium Pharmaceuticals.

DR. DEL TITO: Good morning. My name is Ben Del Tito, and I am the senior vice president of Quality and Regulatory Affairs for Auxilium. I would like to thank the Arthritis Advisory Committee and the FDA on behalf of Auxilium Pharmaceuticals for providing us with the opportunity to discuss our complete drug development program with you; that being AA4500, collagenase clostridium histolyticum.

After my brief introduction, I will turn it over to Dr. Tom Kaplan, who is an orthopedic hand surgeon and one of our Phase 3 clinical investigators, and he will discuss the disease state as well as its current management.

That will be followed by Dr. Tony DelConte, who is Auxilium’s chief medical officer, and he will discuss AA4500 clinical efficacy.

He’ll turn it over to Dr. Jim Tursi, who is Auxilium’s vice president of Clinical Affairs, and he will discuss AA4500 clinical safety and our risk management activities.

And finally, Dr. DelConte will return to the podium to discuss the overall summary of our program.

We use our hands constantly for various tasks in our daily lives from the moment we wake up in the morning until we go to bed at night. Activities such as writing with a pen, typing on a computer or a BlackBerry -- those afflicted with the debilitating disease known as Dupuytren's struggle every day with these same tasks that we take for granted. I’d like to ask the panel to please keep that in mind as we discuss our program with you today.

We’re here to discuss AA4500, collagenase clostridium histolyticum for injection. The proposed indication is the treatment of advanced Dupuytren's disease, and that can be defined as a progressive

disease resulting in a fixed flexion deformity or a contracture in one of several joints, most commonly the last two digits of the hand. A Dupuytren’s cord is an abnormal collagen deposition in the palm of the hand, and it results in the contracture.

Now, the current treatment for Dupuytren's disease is surgery. What we would like to discuss today with you is an alternative to surgery, a novel option for physicians who treat Dupuytren's disease. AA4500 is a new molecular entity, and it’s a first in class biological.

AA4500 consists of two collagenases. These are enzymes that are mixed in a fixed ratio. It’s a naturally produced product by the bacteria -- the gram positive bacterium known as clostridium histolyticum, and the two enzymes are referred to as AUX-I and AUX-II, and these cleave the collagen substrate. Clostridium collagenases act in a complementary manner.

AA4500 dosage form is presented in a sterile lyophilized powder in single-use vials, and it’s accompanied by a second vial which contains a sterile

diluent, consisting of calcium chloride and sodium chloride. The calcium is a required cofactor for enzymatic activity.

A single dose consists of 0.58 milligrams from a single-use vial. Now, this is injected directly into the cord, or intralesionally, and it's followed by a finger extension or manipulation after 24 hours to disrupt the cord. Each cord can receive one injection at four-week intervals, for up to a total of three injections.

As I mentioned, AA4500 is administered by direct injection into the Dupuytren's cord. This consists of a third of the dose injected three times with close proximity into the cord. Once injected, AA4500 acts locally.

This illustrates the complementary activity of AA4500 components. Starting with the left panel, we see the action of AUX-I, which is a Class 1 collagenase, exhibiting activity against intact collagen, cleaving at the ends of the collagen molecule shown here -- this being the amino terminus of the collagen and the carboxy terminus of the

collagen.

Then, AUX-II in the middle panel is a Class 2 collagenase, and this exhibits activity against collagen peptides or fragments of collagen, and cleaves internally on the collagen molecule. Combining these two enzymes to form AA4500 results in a more complete degradation, because cleavage occurs on multiple sites on the collagen molecule.

A few regulatory achievements are shown on this slide. The Investigational New Drug application, or IND, was filed in 1994. An agreement with the agency was made on the dose selected, the .058 milligrams equivalent to 10,000 units during the end of Phase 2 meeting in 2001. Auxilium licensed the product in 2004 with a subsequent IND transfer. Our Biologics License Application, or BLA, was filed in February of 2009, and it was accepted for filing by the FDA with a priority designation in April of 2009.

Joining us in the sponsors panel, we have a few outside experts: Dr. Tom Kaplan, who I mentioned earlier as an orthopedic surgeon, hand surgeon from Indiana University School of Medicine. We also have

Dr. Philip Waller, who is a practicing rheumatologist from Houston, Texas, and we also have Mr. Paul Chamberlain, an expert immunologist from the NDA Regulatory Sciences group in the UK.

Joining us from Auxilium in addition to Drs. Tursi, DelConte and myself are Dr. Ted Smith, who is Auxilium’s vice president of Biometrics, and Dr. Susan Emeigh Hart, Auxilium’s senior director of Drug Safety and Metabolism.

And with that, I would like to turn it over to Dr. Tom Kaplan, who will discuss the disease state and its current management. Dr. Kaplan.

DR. T. KAPLAN: Thank you, Dr. Del Tito.

Before we discuss the data on AA4500, I’d like to take a few minutes with the Committee to review what Dupuytren's disease is, and what our current treatment methods for it are. Dupuytren's disease is a progressive, fibroproliferative disorder that affects the tissue in the palm of our hands and fingers. As it develops, cords and nodules form in the hand contracting the fingers, drawing them down towards the palm. We typically see it most commonly

in the ring and small fingers initially, and see it in patients approximately 50 percent of the time bilaterally.

The pathoanatomy of Dupuytren's disease is that it affects the palmar fascia. This fascia is a layer of tissue underneath the skin that extends up the palm and into the fingers. It’s above the flexor tendons and neurovascular bundles in the palm, and as that tissue in the palm is organized into a triangular configuration, there are these longitudinal bands that run along the palmar fascia. It is these bands that become diseased with progressive collagen deposition, and cords will form in these bands.

As these bands extend up towards the finger, they become somewhat more complex. They’ll bifurcate or trifurcate actually and go towards the web of the digit. They can extend along the sides of the digit, and at this level, will actually wrap around the nerves and arteries as they go up into the finger.

In the early stages of the disorder, fibroblasts begin proliferating and differentiate into the pathognomonic cell of Dupuytren's disease called

the myofibroblast. These myofibroblasts actually have smooth muscle components and have a contractile ability. And this is when we first see nodule formation, and typically in the palm.

In the intermediate phase, the myofibroblasts begin to align along lines of tension in the palm of the hand, and with progressive collagen deposition, cords begin to form. And in the advanced disease, these cords begin to shorten, causing a finger contracture.

Nodules seen here in the palm of the hand most typically are seen over the MP joint in the palm. They are usually painless, but many patients will present at the nodule stage not sure of what is growing in their hand, concerned that it may be something more serious like a tumor or a cancer condition. These usually do not bother patients other than their appearance, but some patients will have pain associated with the nodules, especially if the nodules are particularly active, or patients who have to do a lot of repetitive gripping activities.

Other times, also less common, the nodules

will actually cause an irritation of the underlying flexor tendons, causing a flexor tenosynovitis.

Following nodule formation, we typically see the progression into cords, and you can see these well-defined bands extending up the digits. These cords, as they travel up the palm and into the finger, connect to the skin, and we'll oftentimes see the skin draw down into the hand, forming a pit. They'll go across down towards the joint, causing contracture, and they can course around the nerves and arteries.

As these cords shortened, contractures form. The cords in the palm typically cause contractures of the MP joint, as seen in this patient, where the cord comes down the center of the finger, the big nodule here and draws this joint down into a contracted position. The cords in the finger oftentimes cause contractures of the proximal and distal interphalangeal joints.

The prevalence of the disease varies depending on the population that we're looking at. It's more common in the northern -- in the Caucasian population, particularly patients of Northern European

ancestry. It is a disease of adult life, and affects men much more frequently than women.

The etiology is not completely understood. There have been many associations with Dupuytren's disease, and it’s felt most likely to represent a genetic condition which exhibits an autosomal dominant pattern with variable penetrance. Familial clustering is seen.

Other associations which have been reported in the literature include those that cause tissue ischemia such as smoking and diabetes; trauma, especially manual laborers who may have repetitive microtears of that palmar fascia; epilepsy, where the drugs used to treat epilepsy such as Dilantin and alcoholism.

So what is the impact of Dupuytren's disease on the patient? Well, we know what science and the literature tell us. This is a Sollerman test, which looks at many common day-to-day activities such as putting a key in a lock and turning it, picking up a coin from a table, unscrewing the lid of a jar and buttoning your shirt. What Sinha looked at in 2002

was to correlate the Sollerman scale or test results, the maximum score of which was 80, and what they found was in patients with a less severe contracture, scores tended to be higher. And as the contracture progressed and worsened, their scores tended to deteriorate.

They also correlated this with a postoperative function, and found that the scores would increase again after surgery to correct the deformity.

The patients do the best job of telling how Dupuytren's disease affects them. Most commonly, patients describe difficulties doing their daily activities, particularly with personal hygiene, such as washing their face, combing their hair, tying a tie and shaking hands. It can also affect patients' jobs, particularly patients who have to get their hands in tight spaces, who have to wear gloves for their job or use a keyboard.

And because this is a disease of advanced years, many patients are retired and looking towards their hobbies in their retirement, and can no longer

do the sports that they were looking forward to or enjoying, or hobbies such as woodworking or playing a musical instruments.

Because there’s no cure for Dupuytren's disease, treatment is based upon the severity of the disorder in the patient. Until a patient has a functional limitation of their hand, we usually recommend observation. This can be -- if someone has a painful nodule, oftentimes a massage may be helpful. Occasionally, corticosteroids are used for a painful nodule as well.

But we reserve treatment of the contracture until the contracture is bad enough, because there’s limitations with all of our treatments. A quick test is when a patient can’t get their hand flat on a table anymore, we typically think that their contracture has advanced to the point that intervention is warranted. A rough scale, that’s an MP contracture of approximately 30 degrees, or a PIP joint contracture of approximately 20 degrees.

The current treatment options of surgery are either a fasciotomy, which involves division of the

cord at one or more locations; fasciectomy, which involves excision of the entire diseased cord which is causing the contracture; or a dermofasciectomy, which involves excision of that cord and the overlying skin with it, which then necessitates placement of a skin graft on top of the defect.

This last option is typically reserved for patients who have surgery previously and have had recurrent disease.

Fasciotomy can be performed either in an open end or percutaneously. This is a patient who had a contracture of his small finger at both the MP and PIP joints and was not willing to undergo the rigors of a more formal surgical procedure or the postoperative recuperation necessary. So through three small incisions along the palm and into the finger, we sectioned the cord, and was able to obtain this type of correction we got the MP joint fairly well-corrected. However, you can note there’s still some mild contracture left at the PIP joint.

The problem with a fasciotomy is that recurrence is very frequent. In a study in 1997,

Duthie, et al, looked at 82 patients with an average preoperative contracture of 71 degrees. At ten-year follow-up, one-third of the patients had no further treatment, and their contracture had worsened to the point of 57 degrees. Most interesting is that two-thirds of the patients required further treatment at an average of five years after the index procedure. And by that time, their contracture had worsened to 85 degrees.

This is also being performed more commonly with a needle procedure. The advantage of this is a quicker recuperation, less morbidity associated with the procedure, and you use a small needle in order to section that corridor at one or more locations. Unfortunately, although it’s more tolerable to patients, it still has the problems of high recurrence rate.

In three various studies from 1993 to 2006, recurrence rates varied from 50 to 65 percent at average of three years. It’s also associated with numerous potential complications, as it is a relatively blind procedure. Nerves can be sectioned

as well as arteries. Skin fissuring has been reported as well as flexor tendon injury.

So our current mainstay of treatment in the U.S. is subtotal palmar fasciectomy; that is, excision of the diseased cord which is causing the contracture. You see this is a typical patient preoperatively. He’s asked to open and close your hand, and you see the limitation of both the MP and PIP joint levels. Again, when we think about surgery, when the MP joint can’t extend to more than 30 degrees or the PIP joint, 20 degrees.

This is done in my practice under a regional anesthetic, but can also be done under a local anesthetic with epinephrine. It’s done through a extensile approach. I typically prefer an excision which kind of zigzags up the palm so that we can fully dissect out the diseased tissue. As we mentioned earlier, especially as we get up into the finger, the diseased cord which is seen here can be above the neurovascular bundle which is seen along right here, and kind of spiral around it.

So we need to meticulously dissect out the

nerve and artery, separate that from the diseased cord, and then ultimately, we'll excise that cord where it attaches to the flexor tendon sheath.

After the cord is removed, we then test our results. You know, oftentimes with the MP joint, we're able to get a full extension after excision of the diseased tissue. The PIP joint, however, doesn't always behave as well, and when there is a long-standing and high severe contracture, oftentimes we may still have a limitation of extension at the PIP joint level.

It's a matter of debate in the hand surgery literature of whether it's then beneficial to go in and formally release the ligaments about the PIP joint in order to obtain a better correction, or to try to achieve the rest of the correction postoperatively through therapy.

We get patients into therapy very quickly postoperatively because we don't want them to lose the ability to close their fist, which wasn't a problem to start with. Typically after surgery, particularly with patients who had a very severe contracture, we

may not be able to close all their skin incisions, and areas in the palm may be left open to heal. So if therapists will get involved earlier on in order to help manage the swelling that we always see after surgery, we want to minimize that, because that will limit the patient's ability to move their fingers, we want to start wound care if necessary; and we want to start those range of motion exercises.

Typically, I have patients in a splint full-time after surgery for the first two to four weeks. We kind of leave them in that splint to maintain that extended posture, and have them take it out of the splint every hour or two to work on their exercises. Once they can comfortably make a fist during the daytime, I have them just wear their splint at nighttime for approximately four months so that the scar that's formed after surgery doesn't contract at all and you don't see a recurrent contracture, or limit the recurrent contracture that we see.

This is just an example of a patient who's two days postop, who's moving her fist. This is the same patient who on the previous slide we had fully

extended her fingers, and you can see that she's not able to do that actively. Oftentimes, with advanced contracture of the PIP joint, the extensor tendons may be a little bit loose, they may be a little kind of bound down, may not have the strength to fully open on their own, which is why that therapy's so important.

This is a typical series of subtotal palmar fasciectomy. This is a consecutive series of 109 patients in 2007. And what they found is that with the MP joint, they had a 97, 98 percent initial result. At the PIP joint, it was in the 70 percent range. And when they stratified it by severity, they found that the patients with a low severity contracture, less than 30 degrees, 78 percent maintained their correction at a year. However, patients with a more severe contracture which was greater than 60 degrees, only 50 percent of them maintained their correction that was achieved interoperatively.

Complications with surgery include digital nerve and artery injuries, particularly in recurrent cases; flare reaction, which is similar to complex

regional pain syndrome where the whole hand will become swollen and stiff; infection, loss of the ability to make a full fist and recurrence. And in this study, there was an average of about 20 percent of patients who had recurrent disease at 12 months.

So surgery has some limitations. The incision and dissection that’s required to do the procedure safely leads to postoperative pain, healing response and scar tissue formation. Patients typically require a minimum of six weeks for their scars to settle down, and oftentimes three to four months. Hand therapy has been showed to optimize results. There are complications. It doesn’t cure the disease and recurrence can still occur, and it’s an operation that not every patient is willing to endure.

I find it helpful when talking to patients with Dupuytren's disease or any hand condition, discuss the options with them and to keep these goals in mind. We want to eliminate their contracture. We want to maintain a supple finger for the patients so they can comfortably open and close their fist. We

want to limit the morbidity that they go through, limit recurrence, limit complications and get them back to function as quickly as possible.

I'm excited to be here today as the Committee considers a new, novel option for Dupuytren's disease which will hopefully give us more options for our patients.

I'd like to now bring up Dr. DelConte.

DR. DELCONTE: Thank you, Dr. Kaplan.

My name is Tony DelConte, and I'm Auxilium's chief medical officer. And what I'd like to do this morning is discuss the overall clinical program and clinical efficacy for AA4500.

The clinical development program consisted of 13 studies in over 1,000 subjects who received at least one injection of the .58 milligram dose. These were done in a series of standard Phase 1, Phase 2, which included proof of concept and dose ranging, and then Phase 3 studies which we included as investigators orthopedic hand surgeons, plastic surgeons and rheumatologists.

In the Phase 3 study, there were three

double-blind placebo-controlled studies, and these were all followed by an open-label extension. And we had additional open-label studies and supportive studies for our safety database.

Now, if we turn first to the PK results. This is a series of 16 subjects with Dupuytren's disease who each received one injection, a single injection of .58 milligrams. And sampling was done at baseline and then at least 11 different time points through a 30-day period, and at no time point was any quantifiable systemic exposure noted, indicating that this is local, nonsystemic therapy.

Since the three double-blind placebo-controlled trials were all identically designed, I'll describe them here. A dose of .58 milligrams or placebo was injected into the cord, into the pathologic structure, at each injection cycle. And a cycle consisted of the injection at day zero, and this was followed by the finger extension or manipulation procedure to disrupt the cord 24 hours following the injection.

And then further evaluations were done, and

then finally, at Day 30, an evaluation was done and measurements were done to see if the patient would be eligible to receive an additional injection. And each patient in the trial can receive up to three injections at four-week intervals, and this is the goal to achieve the primary outcome, the primary endpoint is a reduction in contracture to zero to 5 degrees. That’s to get the hand perfectly extended.

And each of the double-blind components of the trials were then followed by an open-label extension to allow patients on placebo to receive active drug.

The key inclusion criteria, these were adults at least 18 years of age who were affected with Dupuytren's disease and a palpable cord, causing a contracture of at least 20 degrees. And for the MP joints, they can go up to 100 degrees. For PIPs, this would be up to 80 degrees.

We excluded patients with bleeding disorders or disorders affecting the hand or any other condition that could confound the results. They could not have received previous treatment within three months prior

to the study start, and we excluded a few certain drugs and allergies to collagenase or any of the components of the product.

The efficacy assessments were done as follows: We measured the hand and the fingers at full extension and then full flexion, and the difference between flexion and extension was then recorded as the range of motion. We used an instrument like this, which is known as a goniometer, and this would be complete extension, and then a contracture of 90 degrees would be to here. And these were done consistently on all of the subjects in the trial.

The patients were then randomized two to one, active to placebo, and there was further stratification done by the joint type, whether these were MP or PIP, and in Studies I and II, also by baseline severity. So we looked at low versus high severity.

Standard safety assessments were done, including the recording of adverse events, antibodies, standard laboratory and vital signs.

Now, the primary endpoint, the primary

outcome of all of the studies, was the proportion of subjects who achieved that correction to within zero to 5 degrees after their last injection, and this was defined as “clinical success” in the protocol. And there were multiple supportive secondary endpoints that were evaluated as well, and this was the proportion of subjects who achieved at least a 50 percent reduction in their contracture angle. We considered this “clinical improvement.” And then the percent change from baseline of the contraction angle was measured. We also evaluated time to success and the change in range of motion.

Additionally, there were global assessments, both physician and patient assessments done, to get an overall picture of the success of the therapy.

And here are the demographics and the disposition of the subjects. In the three double-blind placebo-controlled studies, A57, A59 and 303, which we refer to as Studies I, II and III, more than 90 percent of the patients completed all of the assessments that were required by the protocol. And there was a predominance of men over women in the

studies, and the average age was about 62 to 63. And this is common of what you might see in a population of Dupuytren's patients who present for treatment.

And here are the primary endpoint results in all of the three studies. On the vertical axis is the proportion of patients who achieved success. That's the zero to 5 degrees. And what you see is in the three double-blind placebo-controlled trials, all of them met the primary endpoint and had a greater number of patients on drug versus placebo, where you had very few of the patients. In this largest study, 64 percent on active versus just about 7 percent on placebo.

There were a series of secondary endpoints that were done in a hierarchical fashion, and I'd like to take you through a roadmap of how the secondary endpoints were done. Now, the primary endpoint was the reduction in contracture. But each of these was then taken for all joints first, and we looked at clinical improvement, then 50 percent reduction, percent change, time to reduction, change in range of motion. And these made up Secondary Endpoints 1

through 4.

This sequence was then repeated for the MP joints, and this made up Secondary Endpoints 5 through 9. Again, repeated for PIP, 10 through 14. And this whole series was repeated again not after the last injection, but just after a single injection, and that made up Outcomes No. 15 through 26.

And if we then look at all of this together, we see the three studies and all of the secondary endpoints listed here. And in Study II, we're able to achieve nine additional of these secondary endpoints; Study III, most of the endpoints that were measured were achieved, but Study 1 hit the primary endpoint in all 26 of the secondary endpoints as I had described.

We also looked at the angle or degree of contracture, both before and after therapy for each of the three studies. In Study I, the patients started off about 50 degrees before therapy. And, again, referring to the goniometer, a 50-degree contracture would be to about here. Following therapy, the average contracture was about 12 degrees, or about here.

And then in placebo, they started off about the same place, around 49 degrees, but there was minimal effect on placebo changing contracture. And we see similar results for Study II as well as Study III in terms of fixed flexion contracture.

If we look at range of motion, an important functional parameter, we see that in Study I and Study II, patients started off with a range of motion going through an arc of a little over 40 to 45 degrees. But after therapy, this increased by almost 37 degrees and 35 degrees in Study II, which was statistically significant over placebo. Minimal changed noted in the placebo group.

Now, I mentioned we evaluated the patient and physical global assessments. We looked at treatment satisfaction on a five-point analogue scale. And in this slide for Study I, the percentage of patients who had these results, 87 percent were either very or quite satisfied. And this was statistically significant from placebo, where most of the patients were in the very dissatisfied group. We did the same thing for a physician global assessment of the overall

treatment. And in this seven-point analogue scale, 85 percent of the physicians rated the active treatment as either very much or much improved, compared to 93 percent in the placebo that had no change.

We looked at the durability and recurrence rates. In all of the studies combined, there were 830 successfully treated joints that met the primary endpoint. Thirty of these, or about 4 percent, had a recurrence of contracture, and this is after follow-up in some of the patients beyond one year. Half of these occurred between about three to six months of follow-up, and the mean follow-up period was a little over seven months.

To further assess the long-term follow-up of the recurrence and the durability, we are conducting a follow-up study in all of the patients who were enrolled in the trials who had improvement, and then to see what happens to their contractures after long-term. We also will be assessing the progression of disease in patients who either did not receive treatment or did not have success or a measurable improvement.

So to summarize the efficacy, all of the double-blind studies met the primary endpoint, and that is, more patients on AA4500 achieved this reduction to zero to 5 degrees over placebo. There were multiple supportive secondary endpoints, including improvement in range of motion, which support the efficacy. And both physician and patient satisfaction was significantly better for the drug over placebo. And overall, this provides efficacy comparable to what we see with surgical correction.

I'd now like to bring up Dr. Jim Tursi, who will discuss the clinical safety and the risk management activities that are proposed.

DR. TURSI: Thank you, Tony.

My name is Jim Tursi, and I'm the vice president of Clinical Affairs for Auxilium Pharmaceuticals. You've had an opportunity to witness the demonstrated efficacy profile. Now, we'd like to provide you a comprehensive view of the safety profile, and then I'll follow that by a very detailed look at our proposed risk management activities.

So first considering the safety profile,

I'll begin with an overview of our safety database. We'll consider subject disposition, extent of exposure as well as duration of follow-up. Then I'll speak to the adverse event profile. We'll consider local adverse events, serious adverse events, as well as those additional safety parameters. And lastly, as a biological, I'll speak to the immunologic response to AA4500.

Our pooled safety population is made up of 1,082 subjects that were drawn across studies in our clinical program. They ranged from Phase 1 through Phrase 3 and included both double-blind placebo-controlled trials as well as open-labeled studies.

The disposition of the 1,082 subjects includes a completion rate of 87.6 percent. 12.4 percent discontinued, with the most common reasons: lost to follow-up and withdrawal of consent. Now, the subject age range was quite broad, and it ranged from age 33 to age 90. And subjects may have received anywhere from one to up to eight injections.

In terms of the extent of exposure, that

1,082 subjects represents 2,630 injections. That reflects treatment of 1,780 cords, and that's divided into 1,036 metacarpophalangeal cords and 743 proximal interphalangeal cords.

As to duration of follow-up, the mean duration, 9.5 months, with a minimum of two days and a maximum of 6.7 years. The interjection interval, time between injections, ranged from as short as ten days to as long as greater than 6.4 years.

Next, to the adverse event profile, and as we discuss this, I would ask you to consider the acute and nonsystemic nature of AA4500 therapy. When considering those adverse events that occurred at greater than or equal to 5 percent, the most common: edema peripheral or swelling of the treated hand, contusion and injection site pain, were the three most common. And they ranged from 77 percent to 40.9 percent. The vast majority of these were mild to moderate in severity, with less than 3 percent being considered severe.

The next most common adverse events: extremity pain, injection site hemorrhage, tenderness,

injection site swelling, ecchymosis and skin laceration. And that ranged from 37.4 percent to 12.7 percent. Again, the vast majority mild to moderate in intensity, with less than 1 percent of these adverse events being considered severe.

Finally, completing those to greater than or equal to 5 percent pruritus, lympadenopathy, blood blister, axillary pain, hematoma, arthralgia and injection site pruritus, ranging from 12.7 percent to 5.3 percent. Again, the vast majority were mild to moderate, with less than one-half of 1 percent of this adverse events being considered severe.

There are several important trends to bring forward as it relates to the adverse event profile. The overwhelming majority of adverse events were confined to the treated extremity. Most were nonserious and were either of a mild or moderate intensity. The vast majority resolved prior to the next injection with no further intervention, with a median duration across the entire adverse event profile of ten days.

Next, considering serious adverse events in

the clinical program. There were 92 subjects who experienced serious adverse events. But it's important to point out that if the serious adverse event did not involve the treated extremity, there was a similar proportion between AA4500 subjects and placebo subjects. Nine subjects experienced ten serious adverse events that were considered treatment-related. They included a case of ligament injury, three cases of flexor tendon rupture, a recurrent case of complex regional pain syndrome, a boutonniere deformity, a case of deep vein thrombosis of the lower extremity, a case of sensory disturbance and Dupuytren's contracture in the same subject, and a case of tendonitis.

I would like to spend some time and speak specifically and provide details around the case of ligament injury and the flexor tendon ruptures. The first case was a 61-year-old male who, 43 days following his second injection, noted on his physical exam significant bow stringing. Essentially, the flexor tendons were pulling forward on the skin of the treated finger. He was ultimately diagnosed with an

A-2 and an A-4 pulley rupture, and surgical correction in the form of joint fusion and tenotomy was ultimately performed.

The second case, a 62-year-old male who, six days following his first injection, noted finger weakness. Physical exam and MRI confirmed a rupture of the flexor digitorum superficialis tendon, with an intact flexor digitorum profundus tendon. This subject had a pre-existing boutonniere deformity, and it was ultimately brought to surgical correction of that deformity with no surgical intervention of the tendon rupture at that time.

The third case was a 61-year-old male who, eight days following his first injection, had resumed full normal activities. This included his employment, which required him to lift heavy objects. During employment while lifting a heavy pallet, he noted immediate finger swelling and weakness, and ultimately, MRI and physical exam confirmed a rupture of the flexor digitorum profundus tendon and a partial tear of the flexor digitorum superficialis. The subject underwent tenolysis as repair.

The fourth case was a 76-year-old male who, four days following his third injection, noted an inability to flex the treated finger. Physical exam confirmed rupture of both the FDS and FDP tendons, and ultimately, a two-stage repair with tendon grafting procedure was performed.

Although these four events represent less than one-half of 1 percent of the safety population, it’s clearly important to understand the anatomy of Dupuytren's disease and the underlying flexor tendons. This photograph was taken from an operative correction of a Dupuytren's cord. And just to point out the anatomy, the Dupuytren’s cord in white, and at the base of the ruler is the intact flexor tendon. But the point being that there are areas where the cord is in close proximity to the tendon, and other areas where it is more distant.

These four cases were considered to the effect of AA4500, and as such, is a focus of the risk management plan which I’m going to discuss in just a few moments.

What about additional safety parameters? We

checked laboratory values, including renal function and liver function studies, and the percentage of subjects in the AA4500 group with abnormalities was low, and was comparable to that in the placebo group. In terms of hematology parameters, again, the percent of subjects in the AA4500 group was low with abnormalities, and was comparable to the placebo group.

And finally, we also checked vital sign parameter changes, blood pressure, heart rate, respiratory rate. The number of subjects with clinically meaningful changes was low, and was comparable to the placebo group.

As a biologic product, we would expect to see potentially an immune or an immunologic reaction to treatment with AA4500. First, considering subjects who received a single dose, and to orient you: across the vertical axis is the mean log titer of antibodies, of either anti-AUX-I or anti-AUX-II in green and orange respectively; and across the horizontal axis, the time in months after injection.

And what was demonstrated for both anti-AUX-

I and anti-AUX-II was a peak in antibody titer at approximately two to four months, with a waning thereafter.

When considering subjects who received multiple injections, in this case up to eight injections, again on the vertical axis, the mean log titer, across the horizontal axis, the respective injection number. First, when considering anti-AUX-I, we see an increase in antibody titers that essentially peaks at about the fifth or sixth injection, and then plateaus thereafter. For anti-AUX-II, again, we see a similar pattern, an increase in antibody titer through about the fifth or sixth injection, with a plateau thereafter.

As to seropositivity, the percentage of subjects who have antibodies present, by the third or fourth dose, 100 percent of subjects have antibodies present to anti-AUX-II or anti-AUX-I respectively.

Considering that virtually 100 percent of subjects develop antibodies, the question becomes do these antibodies affect the safety profile of AA4500. So we performed multiple analyses, including examining

the rate, the severity and the duration of the adverse event profile. In addition, we looked for evidence of systemic anaphylactic reactions.

So first, to consider the rate, if anti-drug antibodies were to negatively affect the safety profile of AA4500, we would expect the rate of adverse events to consistently increase with increasing antibody titers. When considering the four most common adverse events, across the vertical axis is the percentage rate of the specific adverse event, which is identified above each table, and across the horizontal axis by injection number. And what's demonstrated is with increasing antibody titers and increasing injections, there is no consistent pattern of increasing adverse events rates with subsequent injections, and thus with increasing antibody titers.

This profile was consistent across the entire adverse profile of AA4500, and demonstrates that there was no consistent pattern between adverse rates and increasing antibody titers.

Then we considered severity of the adverse events. If anti-drug antibodies were to negatively

affect the safety profile, we would expect those subjects with severe adverse events to have higher antibody titers. To orient you: across the vertical axis is the mean line titer of either anti-AUX-I in green or anti-AUX-II in orange, and across the horizontal axis are the cohorts of those that did not experience the adverse event -- in this case, it's swelling of the hand -- or experience the adverse event as mild, moderate or severe.

So when we first consider those subjects who did not experience swelling of the hand, the mean log titer was 3.5. When we then look at subjects who experience the adverse event as mild, moderate or severe, it's clear there's no correlation between adverse event absence or presence, or no correlation between the severity of the adverse event and the antibody titer. That was also found for anti-AUX-II.

Considering those four most common adverse events, contusion, no correlation; injection site pain, again, no correlation; and extremity pain with no correlation. This lack of correlation was demonstrated across the entire adverse event profile,

confirming that adverse event severity does not correlate with antibody titer.

Then we looked at the duration of adverse events. Should anti-drug antibodies negatively affect the safety profile, we would expect the duration of adverse events to increase with increasing antibody titers and subsequent injections. Across the vertical axis, the median duration is days; across the horizontal access, the injection number. And, again, as is demonstrated, there is no consistent increase of adverse event duration with subsequent injections. And, again, these findings were across the entire adverse event profile for AA4500.

Now, that confirmed that the duration of adverse events does not correlate with subsequent injections and increasing antibody titers.

Next, we did a thorough evaluation to look for any signs, symptoms or signals of systemic anaphylaxis reactions in the clinical program. And that was very straightforward. There were none in the clinical program.

So in summary, with a safety database of

nearly 1,100 subjects and an injection database representing over 2,600 injections, the most frequent adverse events were confined to the treated extremity. They were either mild or moderate in intensity, with the vast majority resolving prior to the next injection.

Serious adverse events occurred, including tendon rupture and ligament injury, and that risk is clearly identified and will be a focus of our risk management plan, which I'm going to discuss in much more detail in just a few minutes.

As it relates to routine laboratories and vital signs, there were no clinically meaningful differences demonstrated between AA4500 subjects and placebo subjects. As to immunogenicity, antibodies developed in nearly all subjects, but they do not appear to adversely affect the safety profile.

And finally and importantly, there were no events or signals indicative of systemic anaphylaxis in the clinical program.

In order to ensure that our clinical trial results are accomplished in clinical practice, we've

created a risk management plan which we believe is comprehensive and will be effective in that endeavor. In order to do that, first we must lay out several goals of that risk management plan: first and foremost, to ensure appropriate administration of AA4500. In order to do that, we must recognize potential and identified risks. We must create and implement strategies ultimately to minimize those risks, and we must inform and educate both physicians and patients.

First considering the potential and identified concerns. Clearly, injected-related bleeding in subjects with coagulation disorders would be a risk of any injection therapy, and thus is a potential risk of AA4500 treatment. The potential for allergic reaction with a biological is also a potential risk. Identified tolerability and safety concerns include those localized reactions which I've provided some detail around as well, as the risk of tendon rupture and ligament damage.

As to those potential risks, risk management activities would primarily include labeling of the

product to address these concerns. Injection-related bleeding in subjects with coagulation disorders would be an expected risk of an injectable therapy, so the label will include a caution for use in those with coagulation disorders. Use would not be recommended for those on concurrent anticoagulant medications, and consistent with the clinical program, however, prophylactic low dose aspirin use would be considered acceptable.

As to the potential risk of allergic reaction, the label would include a contraindication for use in any individual with a known hypersensitivity to AA4500. And consistent with most medications, it would include a warning to physicians to prepare to address any potential allergic reactions should they occur.

As to the identified tolerability and safety concerns, I first spoke of the localized reactions. They are common and they're expected with AA4500 treatment. You've heard the most common: edema peripheral, swelling of the treatment hand, bruising and injection site pain. While the vast majority were

mild to moderate with resolution prior to the next injection, clearly, it’s essential that both physicians and their patients know what to expect with treatment from AA45.

Risk management activities as to the local reactions will include product labeling, physician training and patient product information. The product labeling will clearly describe the local reactions. Consistent with the clinical programs, multiple cords should not be treated simultaneously, and only one hand should be treated per session.

Physician training, which I’ll go into much more detail in just a few minutes, will include details of these local reactions. So physicians during the training period prior to use of AA4500 can know what to expect regarding these local reactions.

And patient product information will describe these local reactions in easy-to-understand and detailed language so patients can know what to expect before, during and following therapy with AA4500.

While the four cases of tendon rupture

and/or ligament rupture represented less than one-half of 1 percent, clearly, inappropriate exposure to normal collagen-containing structures can result in lysis of collagen and subsequent to damage to those structures ultimately resulting in possible injury or reduction of functionality.

The risk management plan is quite comprehensive as it pertains to this specific risk. It will include product labeling aspects -- and I'll go into each of these in quite some detail -- physician training and access management program, safety monitoring which is enhanced; and patient education.

So first focusing on product labeling, the product labeling will be quite detailed and very informative for physicians. The intended users of AA4500 are physicians experienced in the diagnosis and management of Dupuytren's disease: hand surgeons, orthopedic surgeons, plastic surgeons, general surgeons with a hand focus and rheumatologists.

The risk of tendon rupture will be clearly identified, and an injection precaution is also

included. And that reads, “Because AA4500 lyses collagen, care should be taken to avoid injecting into normal collagen-containing structures of the hand. Exposure of collagen-containing structures to AA4500 may result in damage to their structures and possible permanent injuries such as tendon rupture or ligament damage.”

As you can see, it’s quite detailed, and physicians experienced in this disease would clearly understand the warning as it is written.

The next component will be physician training, and we believe that physician training is essential for a successful transition from clinical development to clinical practice. It’s first worthwhile to consider the challenges that we face in our clinical program, to provide a little bit of history as to the clinical development program.

This was a new therapeutic procedure for Dupuytren's disease. There was very limited experience with AA4500 in this indication, and we were embarking on a multinational Phase 3 program. So we needed to essentially create a training program which

could be extrapolated from the experience of a very small number of physicians, and ultimately be able to extrapolate that to multiple investigators and multiple sites across multiple countries.

So we provided several injection training options for investigators. The first option was a 30-minute injection training workshop in which some PowerPoint slides were reviewed, as well as a section of our injection training DVD for investigators. The second option was approximately 30 minutes of injection training at the investigator meeting, again composed of PowerPoint slides and a section of our injection training DVD. All clinical trial sites and investigators received a copy of our injection training DVD as well as our injection training manual.

What we found was there was some variability as to the preferred method of training for both primary and sub-investigators. So when we consider first the primary investigators -- and this focuses on Studies 857 and 859 -- of the 21 primary investigators, five attended both the injection training workshop and the injection training portion

of the investigator meeting. Four attended just the injection training workshop, and five attended just the injection training portion of the investigator meeting.

What was evident was the majority of primary investigators attended neither the injection training workshop or injection training at the investigator meeting. All had access to the injection training DVD or manual, with one primary investigator having an opportunity to directly observe a procedure.

As it relates to the sub-investigators, none attended the injection training workshop, two attended injection training at the investigator meeting, and, again, all had access to the injection training DVD or manual, with some having an opportunity to observe from the primary investigator.

It was clear when we spoke with them that they preferred utilizing the injection training DVD and the injection training manual. We confirmed that by meeting with not only our investigators but other practicing physicians, and these included hand surgeons, orthopedic surgeons, plastic surgeons and

rheumatologists.

We reviewed what we had done previously in training methodology, and we specifically asked their advice, discussing their needs and their preferences. And overwhelmingly, they requested a video (and) written training program. They asked that it be clear and comprehensive, informative and accessible, and expanded from the clinical program.

So in order to do that, we created a training program that is broader in scope and content than that which we used to train our investigators. The proposed program will include additional information to help physicians use AA4500 appropriately. It will provide more depth, more examples, more animations and demonstrations based on the experience of our clinical investigators, and completion of training with attestation will be mandatory prior to accessing AA4500.

The training program is composed of an injection training DVD and injection training manual and the program components, anatomy and pathology, product preparation, injection, finger extension, a

frequently asked questions section, and self-assessment questionnaires. This was created with and features demonstrations of appropriate use by physicians with experience using AA4500. A hard copy training manual is also available for those that prefer that method of interaction or training.

In terms of the first component, review of anatomy and Dupuytren's pathology, this will include detailed illustrations to help the physician visualize the relationship between the Dupuytren's cord and other normal hand structures. It will include information on disease progression, as well as information regarding the mechanism of action of AA4500, so physicians can better understand the treatment procedure.

The demonstration of injection and the finger extension demonstrations include details on product preparation, needle placement advice specific to the joint being treated, details around the injection procedure, as well as a detailed description of the extension procedure, with a visualization of cord rupture.

The frequently asked questions section includes questions that are both product- and procedure-specific; questions regarding preparation, injection and finger extension.

In addition, potential and identified risks are discussed as part of the training program, including those local reactions we talked about and the identified risks of tendon rupture.

Also, information will be provided to physicians to ease adverse event reporting, essentially instructions to physicians during training as to how to report adverse events to Auxilium.

Lastly, a self-assessment questionnaire will be included to ensure physician understanding of content.

I would like to show you some excerpts. First, an excerpt from the injection technique section, and what I would ask you to do, realize this is a small excerpt of the draft version of the training materials, and it’s intended for clinical practice, so you will hear a reference to the word “Xiaflex,” our proposed trade name. In addition, I

would ask you to look for the detail, clarity, animation and live representation that's in the video.

(Video played.)

DR. TURSI: As you can see, it's quite detailed. It includes animation and live representation. Now I would like to show an excerpt from our extension procedure video. This includes information regarding those local reactions, as well as details of what physicians can expect during the extension procedure.

(Video played.)

DR. TURSI: As was demonstrated in the video, with complete correction of the hand in this patient was that audible pop, providing physicians with knowledge as to what to expect. What's also evident is some context around these local reactions: bruising, swelling of the hand and contusion.

We believe training will be most effective if it's required in order to access AA4500, and that's the intent of the access management program. Training will be required to access AA4500 by physicians experienced in the diagnosis and management of

Dupuytren's disease. They must attest to completion of the injection training video or manual, and ultimately, they must submit attestation to Auxilium for enrollment in order to receive access.

Diagrammatically, if a physician wants to use AA4500 and they’re not enrolled, they will be referred to physician training. That could be via website, directly via the video or training manual. With completion of training and attestation, they would forward their signed enrollment form to Auxilium, at which point, they would be placed in a central database of enrolled physicians. Once enrolled, they would contact their distributor requesting access to AA4500. The distributor would check the enrollment database to ensure that they’re enrolled. If they’re not enrolled, ultimately, they would be redirected for physician training, and ultimately, for enrollment. If they are enrolled, they would receive access to AA4500.

The next consideration would be an enhanced safety monitoring program, and that would be essential and vital to identify any potential safety signals.

Safety activities will include a safety hotline which will help ease case reporting for physicians. And as I noted, the training program will include information for physicians to improve and ease that reporting.

We'll perform an aggregate safety review by an Auxilium safety physician monthly for the first year, followed by quarterly reviews thereafter.

And in the event of a tendon rupture, we will follow up directly with the physician with a tendon rupture questionnaire. This is a draft version, and certainly, my intent is not to take you through each detail of the questionnaire, merely to provide you a view of the comprehensive nature of the questionnaire, the amount of information requested, and the details that are requested specifically of the document.

No risk management activities will be complete without considering the patients suffering from Dupuytren's disease. So we'll provide multiple portals for these patients to access information. It will include the patient product information leaflet, as I said, written in easy-to-understand language so

patients know what to expect before, during and after therapy. It will include web-based resources, information on the disease state, but also trained physician listings, so patients can determine in their region physicians who've attested to training with AA4500.

We'll provide office-based educational materials and a toll-free patient product information line for further questions.

I've described each of these individual pieces in some detail, but I think it's important to step back and consider the comprehensive nature of this plan, comprehensive to the needs of both physician and patient. It's constructed of many components, to build a strong foundation for the safe and effective use of AA4500 in clinical practice.

At the outset, I spoke of the goals, primarily to ensure appropriate administration of AA4500. We believe our risk management program is comprehensive and will be successful in this endeavor. To recognize those potential and identified risks, it creates and will implement strategies to minimize

those risks. It educates and informs both physicians and their patients suffering from Dupuytren's disease. We believe it creates the optimum environment to transition AA4500 from clinical development to clinical practice.

So thank you, and I would like to ask Dr. DelConte to come up for the final overall summary.

DR. DELCONTE: Thank you, Jim.

Over the last hour, you've heard a lot about AA4500, and I do look forward to an active discussion with members of the Advisory Committee. But before we go into that, first I would like to summarize why we believe that AA4500 should be approved as the first nonsurgical therapy for Dupuytren's disease.

First, we've heard from Dr. Kaplan how Dupuytren's disease is a debilitating condition that affects everyday activities of those afflicted with the disease. He explained to us that the first approach is often observation and reassurance. Once the disease progresses to the point where the patient is willing to have surgery, the results are generally good. Surgery can typically provide relief,

straighten joints and restore function.

However, surgery is not a perfect solution. While most surgeries have a positive result, there's some serious risks and complications that occur, including injury to other structures such as nerves and arteries. There's also risk of infection, scarring and general wound healing issues. In addition, the surgical procedures leave the patient with a prolonged follow-up and recovery period, sometimes requiring extensive physical therapy. And subsequent surgeries to the same area are more complex and involve more risk.

Turning to AA4500, we've demonstrated efficacy in three double-blind placebo-controlled trials, each of which met that stringent primary endpoint of getting to zero to 5 degrees, thus restoring function. And looking specifically at Study I data which was recently published this month in the New England Journal of Medicine, 64 percent of the patients achieved that primary endpoint compared to just under 7 percent with a placebo.

And secondly, the safety profile of AA4500

has been well-characterized, with most adverse events being local, self-limiting and confined to the treated extremity.

And thirdly, in order to generalize the results, we've developed a comprehensive training program that has been designed and modeled after our investigator training, and further enhanced to ensure that the clinical results seen in our trials can be extrapolated with an appropriate population of physicians and patients.

In summary, AA450 will provide the first nonsurgical therapy for managing Dupuytren's disease.

I thank the panel for your attention, and I'd like to join my colleagues now.

DR. O'NEIL: Thank you. We will now have a discussion of the data presented, with the panel asking questions of the sponsor. I would like to ask my colleagues on the panel to please signal a comment that they may have and wait for recognition by the Chair so we don't all talk together, and also remind you to turn off your microphone after you have spoken so we don't have sheer chaos and wild noise.

I would like to begin with a question probably for Dr. Tursi, but also for the pharmacologist involved in the development of this product. Collagenase is one of a large family of enzymes in almost any living organisms that are in a class called serine proteases. These serine proteases are very potent and multifunctional enzymes that do more than what we have named them to do. In particular, the complement system is a series of serine proteases which work one upon another to activate enzymes that have large amplification and very broad complications when allowed to proceed uninhibited in the body.

Collagenase, elastase, complement proteins, thrombin, the kinins are interrelated and one can activate another. There are a number of anti-proteases that control these reactions in the body. I'm wondering if in any of your animal development or in your human studies, you found evidence of complement activation, thrombin activation -- I noticed one of your SAEs was a DVT in a remote extremity -- or other related things.

I suspect a lot of the local edema is from kinin activation locally. Do we have any information about that, because this could -- if the product were injected near or worse still in a vessel, could certainly produce remote reactions.

DR. DELCONTE: Yes, I'd like to ask Dr. Susan Hart, who's our toxicologist, to come up, and she can describe some of the animal findings, including the histologic findings.

Dr. Hart.

DR. HART: I'll speak directly to your question regarding activation of complement or other serine protease pathways. We haven't evaluated these directly in animal studies because there is an extensive literature base on the effects of clostridial collagenases in these pathways. And having reviewed that literature, I found no evidence that the collagenases directly activate complement, directly convert kinin to bradykinin, or directly interfere with thrombin pathways or alter thrombin-mediated pathways.

We haven't seen any indication of that in

the animal studies which have included evaluation of coagulation parameters, hematology, local histology and also systemic histology. So as far as the literature is concerned and our own studies are concerned, there's no evidence that the product itself interferes with those pathways.

DR. TURSI: As to that specific adverse event, I can provide you a little bit more detail, but it did not appear to be related to AA4500 use. This was a 62-year-old male with a history of Lederhose consistent with a diathesis of Dupuytren's disease. And he was based in Australia and drove a considerable distance to the study site. This was approximately two to three hours in each direction. Had received the injection day zero and ultimately noted the lower extremity symptoms of left knee and calf pain two days thereafter. A Doppler revealed a single lower extremity thrombosis, and this was ultimately managed with anticoagulants.

Across the entire clinical program, there did not appear to be evidence of complement activation. In regards to the local events, it's

important to realize the pharmacology of AA4500 may also play a role ultimately in those local reactions. Anti-AUX-I and anti-AUX-II as enzymes are very efficient at cleaving collagen into small fragments. When they do so, especially in the animal studies, we see evidence of increased capillary permeability, hemorrhage, some rapid localized edema and local non-immunologic mass cell histamine release.

So a lot of the symptoms that we're seeing locally could also be explained by the pharmacology. And as I noted across the clinical database, there did not appear to be evidence consistent with your concern.

DR. O'NEIL: Dr. Weisman.

DR. WEISMAN: I have two questions. I'm not sure which of you would address one or the other, but we'll just see.

The first question is, it seems that you've set up a very interesting, almost gatekeeper type of panel to authorize physicians to be able to use this procedure. Who constitutes that panel? How will that panel be independent of marketing efforts? And that

panel would be somehow accountable to a review as to making sure that the review of these individuals who are allowed then or certified to be able to use the product continues on the very high level and is consistent with the collection of data about the results that you're also collecting of the procedure. How will that be arranged?

DR. DELCONTE: I'll have Dr. Tursi address the issue of the access management program, but the types of specialties was designed after the types of physicians who were in the clinical trial program.

DR. TURSI: Thanks. As I noted during the main presentation, the access management program's specific intent is to basically provide access to those physicians who are best-suited to ultimately use the product. One of the first steps ultimately in that access, as I noted, was the physician training component, and the required attestation of that training by the physician that would like to use the product.

To that end, attestation will require specifics that the physician identify their specialty.

If it’s within one of those specialties we’ve described which was hand surgeon, orthopedic surgeon or plastic surgeon, rheumatologist, then the process would move quite automatically, through ultimately providing access to those physicians.

There also would be an opportunity for them to identify themselves as another specialty. If they do, that would then be called to the attention of our internal Auxilium staff, which likely would be through our safety group, at which time we would determine the availability for the drug for those individuals.

So the goal being to provide access ultimately to those physicians best-suited to use it, which would hopefully ultimately achieve the clinical trial results in clinical practice.

DR. WEISMAN: My second question is sort of a derivative of the first, and that is that since the complications that we’re concerned about, such as tendon rupture or ligament rupture, and the fact that shortly after the procedure, many of these patients are going to require a manipulation for efficacy, there would need to be a great deal of expertise of

hand surgery involved either with the procedure itself or as a follow-up of the procedure.

So my question is a conceptual one, and that is, do you consider this a medical procedure or a surgical procedure, and should the individuals that are involved in this whole process be individuals who are specifically used to doing surgical-type manipulation and careful control of these factors rather than internists or rheumatologists who generally speaking are not used to doing these kind of procedures following an injection of this material?

DR. TURSI: We consider this a medical procedure, and we have in our group Dr. Kaplan, who's a hand surgeon who was an investigator, and Dr. Waller, who is a rheumatologist, and who also was an investigator in one of the open-label trials. So I'd like first, Dr. Kaplan, if you can discuss your view of the entire procedure, and then I'll have Dr. Waller come up as well.

DR. T. KAPLAN: I think as you mentioned, there are two main parts to the procedure, one putting the injection in place, and then secondarily, doing

the manipulation, which I agree is beneficial for probably most patients who don't rupture on their own spontaneously beforehand.

As far as doing an injection, it's fairly straightforward, I think, amongst both surgical specialties and rheumatology, internal medicine. Rheumatologists frequently do, to my knowledge, inject Dupuytren's cords. They do do cortisone injections for joints or trigger fingers as well in the hand. So I think that they're accustomed to doing injections even into Dupuytren's tissue. They may be less accustomed to doing manipulations, and I'll let Dr. Waller kind of address his experience with that.

I found the procedure relatively straightforward. As with any new procedure, there is some experience that you gain in the first couple times that you do, and certainly, I think that I've gotten better at it as I've done more of it. But, again, I think it is relatively straightforward, and I think it's something that would not be too difficult to teach or train to perform.

DR. WALLER: To reintroduce myself, Philip

Waller from Houston, Texas, practicing rheumatologist. I do think we've got the knowledge of the anatomy at least from tendons. We certainly have injected trigger fingers, Dupuytren's, de Quervain tenosynovitis, bicep tendonitis. This was obviously a different injection, and actually, almost a simpler injection in the sense that the cord was so different than what we've seen in joint and injecting other soft tissue.

The manipulation itself, I will agree it's not something we do every day in clinical practice. As Dr. Kaplan said, it was a learning process that after really with our first patient, it was a fairly simple procedure -- and certainly no disrespect to the hand surgeons or orthopedic surgeons, I do think we have the experience to do the manipulation, because it did not really require a specific amount of excess training. This video is a completely different video than we initially saw as an investigator, and much more comfortable to watch, in the sense that the training's much easier in this video.

So the answer, yes, I think we can do the

injection. Secondly, the manipulation I do believe can be done.

DR. O'NEIL: The next question is from Dr. Saag.

DR. SAAG: I want to follow up on Michael's comment about what types of providers should be performing this procedure, and tag on to the comment made by the hand surgeon that there's a bit of a learning curve. And particularly, as that relates to the risk management strategy, how can we be sure that by watching a video -- and for those in the room that have been asked to watch videos as part of training, unfortunately, many people are checking their e-mail at the same time while they're surfing on the web on the video. How do we assure that there is adequate knowledge and adequate experience gained just from this video, to avoid a significant learning curve?

And the corollary to that is, do we have any sense from the four cases of tendon rupture and ligament injury about where those events occurred in the experience of the investigator? And are we confident that the risk management program will

mitigate the potential for injecting this potentially toxic compound in areas where it’s not supposed to be?

DR. DELCONTE: Dr. Tursi will answer that question.

DR. TURSI: We believe the risk management plan will effectively mitigate that risk, as I’ve described it. In terms of the first point and the specific physicians ultimately receiving access, we ultimately went to them to ask what do you prefer. Based upon your knowledge of the procedure, based upon your understanding of the disease, what would be the best method ultimately to provide training. And that answer came back overwhelmingly, not just from investigators but also generalists -- and when I say “generalists,” meaning general rheumatologists, general surgeons within the specialties I told you. And that was the feedback we ultimately received.

In terms of the learning curve or the training curve, I would ask Dr. Kaplan or Dr. Waller to come up to speak specific to their example, because these were new physicians at using AA4500. They had not had access to this before. They had never used it

outside of their initial experience in the clinical program. So I think they could probably provide the best representation of what that “training,” looks like.

Dr. Kaplan.

DR. T. KAPLAN: Sure. I think the most important part, honestly, of the training is to highlight the problem, which is tendon rupture. So we have to impart upon the physician they need to be concerned. They need to pay attention. They need to be surfing their e-mail if they’re going to do a new procedure that they’re just learning. As a surgeon, my training, you do it as during a residency. You learn procedures, but even after that, there’s always new products, new techniques that are being developed.

And as a practicing physician, as you know, most of the time, that’s not done in a hands-on workshop, per se. You have the experience that you have through your practice, through your training, and then you can adapt to new tools to your training. This is just one more tool that we’ve utilized.

I had no experience with collagenase prior

to my involvement in the trial. I will say that the first time I did it was -- again, I was kind of comfortable with the injection, but feeling that resistance of injecting into the cord was a new experience. But you knew it right away. It didn't take -- as you did that injection, you had a sense of what that injection was. And if you weren't in that cord and you lost resistance on your plunger, you knew immediately that potentially, you were out of that cord and you needed to stop that injection.

So I think the most important thing to highlight to anyone who's going to do this -- and I do agree with Auxilium that we should limit it to physicians who do understand the anatomy of the hand, and particularly the anatomy of Dupuytren's disease, because those cords can vary in patient to patient.

So we want to make sure we get physicians who are knowledgeable with the condition and who are going to adopt it and utilize a new treatment, and give it the due that it requires to learn it properly.

DR. DELCONTE: And Dr. Waller can also comment on the learning curve, if he could come

up -- because he's done a number of injections.

DR. WALLER: The one question you addressed, I think, or one answer, the tendon ruptures did not occur with any of the rheumatologists doing the injections. As Dr. Kaplan said, the first injection, yeah, it was a little -- it's certainly different, and subsequently, it was much more comfortable after that. I do think Auxilium's doing the best they can for a video.

And as other rheumatologists, I remember when we got our first dose of -- one of our biologic drugs that may be intravenous, we usually weren't set up back 10 years ago to have IV poles, and now we all have essentially, epinephrine, cortisone for allergic reactions. And unfortunately, there were no videos to watch a patient get some of these biologic drugs for us.

So to me, this video is actually again more -- making me more comfortable, and I think other rheumatologists would -- in the sense that it's a potent drug, certainly, but we deal with potent drugs every day. And, again, no video, no follow-up.

Certainly, any of the side effects are based on physicians calling in and making the description or the complaint, if you will, in the sense of what happened. And I think Auxilium's got it set up correctly.

DR. DELCONTE: And just regarding the question you had about the timing of the tendon rupture with regard to experience, there was no correlation to that. One of the three occurred in one of the investigators who was also a Phase 2 investigator. And the numbers were really too small to look at other factors that could correlate with that.

DR. O'NEIL: Thank you. The next question is from Dr. Haque, and then Dr. Buckley.

DR. HAQUE: Thank you. I actually have several questions, so if I could, what I'll do is I'll just ask one now and then if Dr. O'Neil could indulge me later.

This question is directed towards Dr. Tursi regarding risk management. And it's regarding the patient education. Since this is sort of a new type

of procedure that we're going to be doing in the office, I was wondering what your thoughts are regarding creating a standardized consent form, and having that basically enumerate and list very specifically risks and benefits, and having all users provide that to their patients in getting informed consent so that it's not like just giving trigger-finger injections where people are very widely variable in how they approach that with their patients regarding risks and benefits.

DR. DELCONTE: The informed consent has not been part of the risk management program at this point. It's really the extensive patient information, the patient information leaflet and additional information. So we have not included that as part of the program yet.

DR. O'NEIL: Okay. Dr. Buckley.

DR. BUCKLEY: I think we're all trying to understand -- I guess the major concern is about tendon rupture, so I'm trying to understand why does that happen. Does it happen because the needle is put in the wrong place, or even if the needle is put in

the right place, can there be some extravasation that then leads to tendon rupture? And in that same line of questioning, I think all of us who have experience doing corticosteroid injections in hands know that sometimes there's tracking of the corticosteroid back through the skin.

Do you have much experience with what happens when there is tracking of this, or have you tried in animals to specifically put it in to a dermal area and see what reactions are?

And I have one other question after that.

DR. DELCONTE: Well, I'll let Dr. Tursi deal with the question about the tendon rupture, and then Dr. Hart can talk about what we've done, because we've actually misinjected deliberately this into a number of structures, so we can tell you what happens with that.

DR. TURSI: As to the specifics of the tendon rupture, there's no way to determine exactly what happened in terms of causing that rupture. We clearly attribute it to AA4500. Whether it was directly injected into the tendon or if it was

injected in the proximity of the tendon is unknown based on the specifics of the procedure.

So, again, although those numbers were small, it was something that was very important to us, and clearly is a key focus of our risk management plan.

I will ask Dr. Hart to come up and speak a little bit about the non-clinical work that you had asked about.

DR. HART: I'm going to point you to the results of two of our non-clinical studies, one of which will address your question on extravasation, and the other which will address your question of misplacement of the injection. The results are similar in both studies.

To address extravasation, I'm going to refer you to the first of these studies, which was our rat intravenous toxicity study. It was clear from having observed the injection sites histologically that in a few of these animals, there was some extravasation from the IV injection site. And in this location which is the rat tail, the injected veins are in very

close proximity to the skeletal muscle, the tendons, the arteries and the bones of the tail. So we basically had all of the structures represented that you'd see in a finger.

No effects on the injected vessel itself. Where it had extravasated, there were no effects on the tendon fibers directly, although the peritendon had lysed in some of the higher-dosed animals. The nerves, the arteries, the skeletal muscle, the bone and the collagen were all histologically normal. And when those tendons that had had the peritendon's lysis were evaluated two weeks later, there was evidence that that change was reversing.

And to answer your question about inadvertent administration, missing the cord and putting it into a subcutaneous location, I'll refer you to a series of three studies that were performed to support a different indication but will answer your question in terms of Dupuytren's disease, because the location is very similar. It was submucosal in the penis adjacent to the vein-artery nerve complex, as well as in different places. When the material was

injected submucosally or into the adventitia of the penis and overlaying the tunica albuginea, which is a dense collagen structure similar to a tendon, there was no evidence that leakage went down into the tunica albuginea and caused any lysis.

We did see the same sort of effects that were seen in the clinic, red blood cells and swelling, but no effects on arteries, on nerves and on larger veins. Only the smaller venules were disrupted. There were some changes in the walls of the arteries, some collection of red blood cells that was not associated with any damage to the smooth muscle, or interestingly, to the periarterial collagen. And that was verified by using a special stain, trichrome, which highlights collagen and collagen damage.

And, again, I want to point out that all of these effects reversed following withdrawal of the compound. There were no permanent effects in those arteries, even where this red blood cell accumulation occurred.

So we've evaluated extravasation. We've evaluated direct misadministration. And in all cases,

normal structures were spared, and in all cases, the changes reversed within two to four weeks following administration.

DR. BUCKLEY: And do you have any specific intradermal injections? You have extra -- but have you actually looked where you specifically put it intradermally?

DR. HART: Intradermally?

DR. BUCKLEY: Yeah.

DR. HART: There was a study done in support of that by the originator company. There was no histologic evaluation done, unfortunately. There's subdermal injections that were published in the literature. And, again, the same spectrum of changes is described, which is the inflammation, the bleeding and the reversibility of the effects. But those investigators didn't specifically talk about blood vessels and nerves.

I can tell you from the dog study that there was no upstream effects. In other words, the overlying mucosal cells and the interaction between the skin and the basement membrane were histologically

normal.

DR. T. KAPLAN: I was going to take an opportunity to kind of share with you clinically what we experienced. When tendon ruptures start -- before this multi-center Phase 3 trial, no tendon ruptures had occurred with the use of collagenase. So shortly after -- I don't know exactly how many months, but within the first several months after the study started, that two tendon ruptures occurred. And in response to that, we kind of as investigators got together to try to figure out was there any kind of pattern, is there anything that may be putting it more at risk?

There have only been two out of 1,000 patients, so it's hard to draw conclusions. But those first two were both in the small fingers when treating PIP joints. And we know that as that cord kind of extends out toward that digit, as that cord gets closer and closer to the PIP joint, it gets closer and closer to where the flexor tendon system is. So certainly, it would affect -- with the way this drug works, that if it does get close to the tendon system,

then it could potentially cause risk and weakening of that system.

So we as investigators got together and we kind of went through the injection technique, made some clarifications to kind of tell investigators, hey, we should really stay away from into the finger area. And when treating a PIP cord, really target it near the base of the finger.

This is just kind of -- this is a slide that Dr. Tursi had shown of kind of that distance between the cord and that flexor tendon system. And, again, in the small finger which is not seen here, oftentimes, there’s a central cord that comes down the center of the palm and goes right down the midline of the digit, which is clearly accessible and oftentimes will separate fairly far from that flexor tendon system.

In the small finger, oftentimes, there’s something called an abductor digiti minimi cord, which is along the side of the digit. Some patients will actually have both of these cords, which will then kind of form a confluence as it goes over the --

around the PIP joint and just proximal to that.

So those are areas we felt that the injection, you have to be a little more careful or move that injection away from those areas to keep it away from the flexor sheath.

And then in the second question, as far as extravasation out of the skin, I certainly experienced that when I was doing it. I was much more happy. I definitely didn't want to extravasate deep to the cord, and some material would come up out of the skin. The only kind of side effects I saw from that, some patients did have some formation of blood blistering in the skin. That could have been due to the swelling that, we see that with fracture blisters. So it could be related to the swelling.

But potentially the collagenase, is hard to know. But when extravasated, usually, that cord is so close to the skin, you could actually see it leaking right through the skin.

DR. BUCKLEY: And just as a follow-up question to all this, it's clear with some experience and good understanding of the anatomy, there's a

learning curve. But for those who are less experienced, have you thought about things like ultrasound guidance?

DR. T. KAPLAN: I think that was actually done in some of the earlier Phase 2 trials, that you looked at ultrasound to map out the cord, to look at the distance between the cord and the tendon sheath underneath of it. Honestly, when you see patients with Dupuytren's disease, the cord is just right there. It’s right underneath the skin, and it’s hard to miss. So it’s very easy to identify the cord and to get the injection to the cord. The key is not getting through the cord and putting the injection deeper to that or from the side.

So I personally don’t feel that ultrasound would be all that beneficial in giving me better definition of the cord and where it is, because I think it’s palpable.

DR. O’NEIL: Thank you. The next question is -- we’ll go back to Dr. Haque and then Dr. Swartz and Ms. Aronson.

DR. HAQUE: I had a question regarding the

basic science that was presented earlier on, I think, Slide 9 regarding the collagenase types. So am I correct that the Class 1 and Class 2 collagenase don't have anything to do with Type 1 versus Type 2 collagen? They're just separated by where they cleave the collagen fibers, and what types of collagen do they work on? Have you seen any injuries to joint surfaces or other structures as well?

DR. DELCONTE: To answer your question, I'll have Dr. Hart talk about the types of -- that is different than the types of collagen, and the types of collagen that the AA4500 has a preference for, a selectivity is Types 1 and Type 3. And Dr. Hart can describe that a bit more.

DR. HART: Your question about the collagenase classes relates to the -- there are two different forms of the enzyme that are secreted by the bacterium. Each is a separate gene product. They're a little bit different structurally, but they don't determine the substrate specificity. Either one has the same substrate preferences. They're active in a test tube against a wide variety of collagen subtypes,

but in vivo, it appears that their activity is somewhat selective for the fibrillar collagens, which is Type 1 and Type 3, with sparing of globular collagens such as Type 4, Type 6 and Type 8. And that, I think, translates to the effects we saw in the animal studies where there was no degradation of the periarterial collagen, which is primarily Type 4.

And if you had a second question, could you please repeat it?

DR. HAQUE: I think that was essentially it.

DR. HART: Thank you.

DR. O'NEIL: The next question is from Dr. Swartz, and just because he will be speaking to someone behind him, I'm going to remind him to speak into the microphone.

DR. SWARTZ: Thank you. I have two questions and a comment. First, most patients who come to my office with this condition have it in a mild form. They may have a nodule that may or may not be painful. They may have an early contracture. And our advice to these patients is that we don't know if it's going to be progressive or not. And so

observation, as has been mentioned earlier, is the most often the first encounter and the first advice to these patients, and they come back when it's more significant.

But with this medication, I can envision that our inclination is going to be to recommend that we treat them without knowing that in fact, they will have a progressive condition, and treat them before the contracture of the MP joint is more than 30 degrees or the PIP joint more than 20 degrees. So my question to the FDA panel as well as to the Auxilium people is would this be considered an off-label treatment, and is this going to be -- and I guess, a better question, will there be a long-term focus and study of these patients to see if in fact, it does prevent progressive disease? That's my first question.

And then the second is, we haven't heard too much yet about the PIP joint contracture. On the opposite side of the spectrum is a severe contracture of the PIP joint to 70 or 90 degrees. And what has been the effectiveness of the injection in the PIP

joint patients to relieve that degree of contracture? Because I think this is where the most trouble is going to be seen. It's pretty straightforward, I think, to inject the palmar cord in the mid palm, but trying to relieve that PIP joint contracture where the spiral cord goes around the digital nerve and where you have a confluence, not only in the little finger but in the ring finger as well, of multiple abnormal structures surrounding the flexor tendon.

So we may want to see a stratification of patients and who's going to treat them based on the degree of severity, particularly in the PIP joint.

DR. DELCONTE: Let me address that second question first about the differences in joint and severity. We did a sub-analysis, and if we had the slide up, we can show you that in the two large multi-center studies, this is the responder rate here, the proportion of patients, and these are the four different subtypes.

And what you see first of all that is in the left two columns, the MP joints generally do better than the PIP joints. And joints generally of low

severity tend to do better than those of high severity. So in the high severe -- and we only stratified this. We sort of broke it in half, less than or equal to 40 and greater than 40. Here, about a quarter of the patients will achieve this zero to five degrees.

So this is what we see in the pooled studies. And when we were talking to and looking at the literature in hand surgery, it is that PIP joints generally as particularly the ones of high severity do not tend to correct as well.

Then furthermore, to answer the question about the labeling and where this would be used, as you saw, the clinical trials used a less than -- a contracture that was greater or equal to 20 degrees. And we would not be seeking an indication specifically for nodules. We would be only where there’s a contracture and in most cases, the patients wouldn’t be coming in unless they had some functional disability as well.

Regarding long-term follow-up, we do propose looking at a two- to five-year follow-up of not only

joints that have been treated, but joints that have not received therapy, to look for a progression. So we'll gain some additional information about the natural history of the disease. And what we understand from the literature is about half the patients with an early contracture or nodule will ultimately go on and progress. But this will give us some additional information on durability, on overall progression in untreated joints, and some additional long-term safety data.

DR. O'NEIL: Our next question is from Ms. Aronson.

MS. ARONSON: I'd like to start with an appreciation of the presentation. I found it very helpful as well as the briefing document. I also thought the video was a wonderful tool that could be used for continuing reference as physicians learn to use the product.

I was left with one question, and that is if there is a slide about exclusion of patient population. I know that Dr. Tursi talked about patient population, and Dr. DelConte referenced drugs such as

tetracycline and anticoagulants that were omitted. But he also said “other drugs,” and I’m wondering what those other drugs are, and if they coordinate with the patient population that might have been omitted from the trial.

DR. DELCONTE: Let me put this slide up on our exclusion criteria that you referred to. And there were really two classes. Tetracycline, antibiotics were excluded because of a theoretical concern about inactivation of the collagenase. And this was just historically carried out through the studies.

The second class of drugs were anticoagulants, and this was because we know you could get some bleeding and bruising at the site. Other than we did allow low dose aspirin, but if a patient was anticoagulated, they were not allowed to be in the trial. And that would be also reflected in the label, and how we would suggest this be used.

MS. ARONSON: Patients with rheumatoid arthritis, for instance, would also be included in the trial?

DR. DELCONTE: In the clinical trials, we didn't want any types of illnesses that would confound measurement. So if they had any appreciable deformity or contractures of their fingers, we did exclude that patient population so that we'd be able to identify just the impact of the drug and not have any confounding from other diseases. So they were not included.

DR. O'NEIL: Dr. Mazor.

DR. MAZOR: This is a bit of a follow-up on Dr. Haque's question. And it relates to informing patients of the risks and benefits of the procedure. And you've talked some about the patient information packet, or however you refer to that. I'm wondering when that would be given to the patient, because I think there's a difference when you get something, look at this and stick your hand out kind of thing versus look at this, think about it and come back and tell me in a week or whatever amount of time.

DR. DELCONTE: Dr. Tursi can address the informed consent.

DR. TURSI: Ultimately, that would be at the

discretion of the individual physician, but as having been a physician in practice, I agree with you. Clearly, there is an advantage to providing patients with this information well in advance of any proposed procedure. So clearly, what we're trying to do as part of our overall risk management plan is not just rely on that patient product information leaflet, but also provide information to patients via website and other patient information brochures that would be available in physician offices. So they could gather that information, have a chance to digest in advance of the procedure.

DR. MAZOR: So I'm wondering -- and this kind of fits with the physician packets as well, because one could envision that the physician training materials or the physician attestation or commitment could include a commitment to informing patients in this way.

And related to that, I wondered about, there's kind of one way to find out if I know something and you ask me, and I can say yes even if I don't, and there's another way, which is you have some

level of testing me. You ask me some simple questions about do you know where to report an adverse event, kind of how can you find this information. Do you know when we recommend that you give this information? So like a lot of continuing medical education, some very straightforward questions that might be a part of that attestation.

DR. TURSI: Yes, we share your concern, and we absolutely appreciate your advice in that regard. I can show you the part of the draft attestation that I think directly addresses your question. At the bottom, we specifically ask physicians, “I will counsel each patient on the risks and benefits of AA4500 and provide each patient with the patient package insert.”

So clearly, we are familiar with that issue, and we clearly want to provide as much information as possible, not just to physicians but to patients as well.

DR. O’NEIL: Thank you. We have now reached the witching hour, and we will take a short 10-minute break. Committee members, I’d like to remind you that

there should be no discussion of the meeting topic during the break among yourselves or with any member of the audience.

And we will resume promptly at 10:45.

(Whereupon, a recess is taken.)

DR. O'NEIL: Now, I'd like to call on Dr. Eric Brodsky, who is a clinical reviewer at DAARP at the FDA, who will begin the FDA presentation.

DR. BRODSKY: Good morning, Advisory Committee members. Good morning, members of Auxilium. Thank you for coming. My name is Eric Brodsky. I'm a medical officer at the FDA. The FDA appreciates your time and your efforts in helping us, advise us, about Auxilium's proposed application for Xiaflex, with the established name of collagenase clostridium histolyticum, for the proposed indication of advanced Dupuytren's disease.

During my presentation, I will discuss the major efficacy and safety results of the application; I will highlight investigator training in the clinical trials and the proposed training of clinicians if Xiaflex were approved. And I will also provide a

benefit/risk assessment based upon the clinical trial data.

Auxilium presented a detailed background regarding Dupuytren's contracture. Auxilium also presented a detailed background of Xiaflex. Thus, I will only add that in 1996, Xiaflex was granted an orphan designation for the treatment of advanced Dupuytren's disease. In general, products can be given an orphan designation for specific indication if the disease will likely affect fewer than 200,000 patients in the United States.

I will also emphasize that Auxilium proposes that Xiaflex be given by a physician experienced in the diagnosis and management of Dupuytren's disease.

There were six randomized double-blind placebo-controlled trials of Xiaflex in patients with Dupuytren's contracture. The only difference between our assessment and Auxilium’s assessment of these trials is that we believe the two largest trials, with many sites and many investigators, served as the primary supports for the efficacy and safety of Xiaflex in Dupuytren's contracture. These trials are

Studies AUX-CC-857 and AUX-CC-859, abbreviated here as Studies 57 and 59 respectively.

Study 57 had a total of 308 treated patients at 16 U.S. sites. Study 59 had a total of 66 treated patients at five Australian sites. In these trials, patients must have had a fixed flexion contracture of at least 20 degrees of an MP joint or a PIP joint caused by a palpable cord to be included. Patients may have received up to three injections of Xiaflex or placebo directly into one cord given at four-week intervals. If the contracture persisted 24 hours after the injection procedure, the investigator extended the treated finger in an attempt to rupture the cord. Additional support for the efficacy and safety of Xiaflex in the treatment of Dupuytren's contracture comes from four smaller randomized double-blind placebo-controlled trials, abbreviated as Studies 02, 03, 51 and 53.

I will focus the efficacy presentation on the results from the two trials that served as the primary support for the efficacy of Xiaflex in the treatment of Dupuytren's contracture. The primary

efficacy endpoint for Studies 57 and 59 was the proportion of patients that achieved a reduction of the contracture of the primary joint, MP or PIP joint, to zero to 5 degrees 30 days after the last injection, where up to three injections could have been given.

Essentially, we are measuring the proportion of patients who achieve a straight joint, which is a clinically meaningful endpoint. In both trials, a statistically significantly greater proportion of Xiaflex-treated patients compared to placebo-treated patients achieved the primary efficacy endpoint after up to three injections.

In Study 57, the U.S. study, 64 percent of Xiaflex-treated patients, compared to 7 percent of placebo-treated patients, achieved the primary efficacy endpoint. In Study 59, 44 percent of Xiaflex-treated patients, compared to 5 percent of placebo-treated patients, achieved the primary efficacy endpoint.

For the Xiaflex-treated patients, the mean number of injections required for clinical success was 1.7 in the two trials. It’s important to note that

the proportion of Xiaflex-treated patients who achieved clinical success after the first injection was 39 percent in Study 57 and 27 percent in Study 59.

After up to three injections, Xiaflex treatment resulted in a greater mean decrease in the mean percentage change from baseline in the contracture of the primary joint. In Study 57, the baseline contracture was about 50 degrees. After Xiaflex treatment, the contracture was about 12 degrees, resulting in a 79 percent reduction in contracture degree. In contrast in Study 57, placebo-treated patients demonstrated a 9 percent in contracture reduction. The results from the Australian study, Study 59, were similar to the U.S. study for this endpoint.

This is a representation of the efficacy of Xiaflex in the treatment of Dupuytren's contracture. These results are based upon the results from Study 57. The white line represents a normal situation, where patients could extend their finger completely without a contracture, zero degrees of contracture. The yellow line represents the mean baseline severity

of contracture in Study 57, which was about 50 degrees. This is prior to the injection. The green line represents the mean degree of contracture after up to three Xiaflex injections, which is about 12 degrees. For Study 57, the contracture was reduced close to normal after Xiaflex treatment.

Contracture reccurrence is a concern for any treatment for Dupuytren's disease because of the nature of the disease, which is progressive and incurable. Few Xiaflex-treated patients in the studies experienced a recurrence, approximately 4 percent. However, the follow-up period was very limited. The mean time of follow-up was about seven months. In the Xiaflex studies, recurrence was defined as a return of the contracture greater or equal to 20 degrees associated with the presence of a palpable cord in patients who initially experience clinical success.

In an attempt to provide some perspective on the incidence of recurrence following Xiaflex treatment, we looked at the published literature for the incidence of recurrence from the most common types

of surgery for Dupuytren's contracture: fasciotomy and fasciectomy. Fasciotomy, as mentioned before, is a division of the cord and is usually done percutaneously. Fasciectomy is a more-extensive procedure, in which the disease fascia and sometimes the normal surrounding fascia are removed.

Using a more-severe definition of recurrence, severe enough to require another surgery, with a much longer duration of follow-up, ranging from two years to about 10 years, we found a wide range of recurrences after surgery. The incidence of recurrence ranged from zero percent following dermofasciectomy, which is a more extensive form or type of fasciectomy, to up to 66 percent following fasciotomy.

One concern is that physicians with different expertise may have different efficacy results. To shed some light on this issue, we performed an exploratory subgroup analysis using the primary efficacy endpoint by expertise of the investigator who performed the injections. In pooled Studies 57 and 59, the majority of the injections were

performed by hand surgeons. Approximately 81 percent of the injections were performed by hand surgeons, whereas about 15 percent of the patients were injected by orthopedic surgeons, and about 4 percent of the patients were injected by rheumatologists.

Within each study, investigators irrespective of specialty obtained similar results for the primary efficacy endpoint, as you can see here. Although there were no major differences in efficacy results for each of the specialty groups, no definitive conclusions can be drawn because of the limited number of patients who were injected by non-hand surgeons.

Now let’s turn our attention to the safety assessment. There were two populations used for this safety analysis. First were patients in the randomized double-blind placebo-controlled portions of pooled Studies 57 and 59 through Day 90. In this pooled safety database, about 250 patients were treated with Xiaflex, and 125 patients were treated with placebo. The Xiaflex dose was .058 milligrams.

The safety of Xiaflex was also evaluated in

the controlled and uncontrolled portions of all 12 submitted Xiaflex studies. In this pooled safety database, about 1100 patients were treated with Xiaflex, representing about 2600 injections. The mean duration of safety follow up for these patients was about 10 months. About 60 percent of patients received two or more Xiaflex injections. You can see the distribution of Xiaflex injections within this table.

We analyzed the safety of Xiaflex in the controlled portions of the pooled Studies 57 and 59 who received up to three injections of study medication. No one died in the controlled period. There was a slightly greater proportion of Xiaflex-treated patients compared to placebo-treated patients who had a serious adverse event. This difference was entirely due to serious adverse events of the injected extremity.

A slightly greater proportion of patients had an adverse event leading to discontinuation, or a DAE. Two of the three patients in the Xiaflex group who had an adverse event leading to discontinuation,

the adverse event involved the injected extremity. Almost all of the Xiaflex-treated patients had an adverse event. The Xiaflex group had two times the number of adverse events compared to the placebo-treated group, patients after up to three injections.

We also analyzed the major safety results in the controlled and uncontrolled portions of the 12 submitted Xiaflex studies on a per-patient basis, the upper portion of the table, and on a per-injection basis, the lower part of the table. In the controlled and uncontrolled portions of the studies, five patients died. The causes of death in the Xiaflex clinical program appear to be consistent with what might be expected for the underlying patient population.

Eleven Xiaflex-treated patients had a serious adverse event of the injection extremity. Of these 11 patients, as mentioned before, three had a flexor tendon rupture, which were likely related to Xiaflex treatment.

We evaluated all the deaths that occurred in the 12 submitted studies and in the pilot academic

study. There were seven deaths. All these patients received a 0.58 milligram dose of Xiaflex. There were no deaths in a limited number of placebo-treated patients. The seven deaths in the Xiaflex group were not expected, given the background co-morbidities of these patients. There appeared to be no relationship between the number of Xiaflex injections and the incidence of death. Finally, most of the deaths occurred six months after the last Xiaflex injection.

All the serious adverse events of the injected extremity occurred in patients who received 0.58 milligrams of Xiaflex. The upper part of the table shows the serious adverse events during the controlled portions of Studies 57 and 59 through Day 90, and the lower part of the table shows the serious adverse events of the injected extremity in the open-labeled uncontrolled portions of the Xiaflex studies.

Of the 11 serious adverse events shown, seven, or 64 percent, occurred within two weeks of the last injection. Many of these patients required surgery or other medical therapy to correct this

serious adverse event. Of these 11 serious adverse events, three were flexor tendon ruptures, as mentioned by the applicant. All of them occurred within seven days of the last injection.

All three tendon ruptures occurred after Xiaflex was injected into a cord affecting the PIP joint of the fifth digit. All the tendon ruptures were likely related to Xiaflex treatment.

Other serious adverse events of note included a pulley rupture, as mentioned before, and complex regional pain syndrome, as mentioned before.

To see if the frequency of the serious adverse events involving the injected extremity was in the same ballpark as surgical complications following surgery for Dupuytren's contracture, we performed a literature search of surgical complications following fasciectomy and fasciotomy. The incidence of intraoperative complications such as arterial injury or nerve injury was approximately zero to 10 percent, and the incidence of postoperative complications range from zero to 18 percent.

The incidence of serious adverse events of

the treated extremity observed in the Xiaflex studies did not appear out of proportion to the incidence of surgical complications as reported in the published literature.

After up to three injections, two times as many Xiaflex-treated patients than placebo-treated patients had an adverse event. The overwhelming majority of Xiaflex-associated adverse events were local reactions. The most commonly reported Xiaflex-associated adverse events were hand edema of the injected extremity, contusion, injection site hemorrhage and extremity pain. These events were likely related to Xiaflex injection. After one injection, 95 percent of Xiaflex patients had an adverse event.

Xiaflex contains foreign proteins, so allergic reactions would not be unexpected, particularly with repeated exposures. However, there were no severe reactions, including those associated with respiratory compromise, hypotension, or end-organ dysfunction.

We performed an exploratory analysis of

pruritus adverse events. Xiaflex-treated patients had a greater proportion of pruritus adverse events compared to placebo-treated patients in Studies 57 and 59. The incidence of pruritus increased in the Xiaflex treatment group with more injections. Thus, there's some evidence of mild allergic reactions associated with Xiaflex injections. However, there were no severe allergic reactions.

As mentioned previously, Xiaflex contains foreign proteins. Therefore, we would expect to see antibodies to both components of Xiaflex, AUX-I and AUX-II. We looked at the frequency of these antibodies and evaluated if they had any clinical consequences. After the first injection, approximately 86 percent of patients had positive antibodies to AUX-I and/or AUX-II. After the fourth injection, all Xiaflex-treated patients had antibodies to AUX-I and AUX-II.

However, there appeared to be no effects of these antibodies on the efficacy or safety of Xiaflex. Patients who developed neutralizing antibodies to AUX-I or AUX-II had similar efficacy as patients with

neutralizing antibodies.

Now I'm going to talk about special considerations for this application. Since the clinical trial results were based on experienced investigators who were highly trained in Xiaflex injections, it is important to compare the training of the investigators in the clinical trials to the proposed training of clinicians if Xiaflex were approved.

As mentioned by Auxilium, no hands-on training such as simulations were performed in preparation for the trials, and no simulations are planned for clinicians in practice if Xiaflex is approved.

As mentioned by Auxilium, investigators in Studies 57 and 59 received training manuals and DVDs. Auxilium also proposes to provide clinicians with manuals and a narrated video, as you've seen. Investigators in the trials attended workshops and meetings regarding injection technique, although not all investigators participated, as you heard before. Instead of these type of workshops, Auxilium proposes

to provide personal liaisons to clinicians in practice.

In addition to the stated training for clinicians, Auxilium proposes additional risk minimization in the form of a managed distribution program that requires a physician to sign a form prior to receiving Xiaflex. Physicians must agree that they understand injection procedures and the risks of Xiaflex injection, including tendon rupture. If physicians do not sign the form, Xiaflex will not be provided.

Now I'm going to assess the benefits and risks of Xiaflex as seen in the clinical trials. The benefit-risk assessment of Xiaflex is based upon the pooled results of the controlled portions of Studies 57 and 59 through Day 90, after up to three injections of study medication. These results may not be reflective of results in clinical practice. Nonetheless, this assessment may be useful as a starting point for your discussions.

Starting with the benefit of Xiaflex, note again all these benefits are based upon after up to

three injections. In the pooled clinical trials, again after up to three injections, two patients needed Xiaflex treatment to obtain the benefit of a straight joint in one patient. Also, after up to three injections, one patient needed Xiaflex treatment to obtain the more modest benefit of improvement of 50 percent of the contracture degree in one patient.

Now moving on to the risks of Xiaflex, again note all the risks are also based on up to three injections of study medication in pooled Studies 57 and 59. One patient needed Xiaflex to have one patient develop a local adverse reaction such as hand edema, contusion or pain of the extremity.

Now for the more serious events. 125 patients needed Xiaflex for one patient to have a tendon rupture, and 83 patients needed Xiaflex treatment for one patient to have a serious adverse reaction other than a tendon rupture, such as complex regional pain syndrome or a pulley rupture.

In summary, results from the controlled trials demonstrate a statistically significant increase in the proportion of patients achieving

almost complete contracture reduction when treated with Xiaflex compared to placebo. Xiaflex injection was associated with twice as many adverse events compared to placebo, with most being local reactions. Serious adverse events including tendon ruptures were not common. Clinical trial results may represent a best case scenario, where the investigators had extensive professional training and were highly trained in Xiaflex injection and finger extension procedures.

Thank you.

DR. O'NEIL: Next, Dr. Kathryn O'Connell will speak to us about risk management considerations in the FDA approval process.

DR. O'CONNELL: Good morning. My name is Kathryn O'Connell. I'm with the Office of Surveillance and Epidemiology at FDA, the Division of Risk Management.

The FDA's concept of risk management is actually the overall and continuing process of minimizing risk throughout a product's life cycle to optimize the risk/benefit balance. And the reason

that the Division of Risk Management is here today is because there is a risk management issue that we've already talked about this morning, and that pertains to training, the role of training, and is required training necessary for safe use of this product.

It's an issue because the relationship between tendon rupture and improper administration of the product is unknown, and there's several factors that go into that. One is the generalizability of clinical practice of trial results that are obtained by highly trained investigators, and another issue is the unknown relationship for this product between tendon rupture and user factors such as specialty or hand anatomy expertise. And then there's the inherent potential damaging effect of the collagenase on collagen-containing structures adjacent to the cord. And your handouts should say the Dupuytren's cord.

In general, risk management for product safety issues are managed through the product's package insert, which all products have. Sometimes the sponsors provide extra education or training. Sometimes, there's post-marketing studies that are

involved, and there's always post-marketing surveillance.

However, if the seriousness of risk associated with any product or with this product specifically make it necessary to require and enforce training, then the Food and Drug Administration Amendments Act, or FDAAA, as you've probably heard it called, does provide FDA with the authority to require something called risk evaluation and mitigation strategies, or REMS. And accordingly, REMS can be required if and only if the FDA determines that these strategies are necessary to ensure that the benefits of the drug outweigh the risk.

REMS in general include one or more of the following: One is a patient medication guide. Second is a communication plan, and that's for healthcare professionals. And the last one is something called Elements to Assure Safe Use, and I'll talk more about that in a minute. But these often involve some form of restricted distribution. That may be how you've heard them referred to.

The first, the medication guide, this

provides for FDA-approved patient-friendly labeling, and it's required. The person who dispenses the product is required to give this to the patient. A patient medication guide can be required by the FDA if the FDA determines that one or more are true: First, is that patient labeling could help prevent a serious adverse event or events. The second is that the product has serious risks that could affect the patient's decision to use or continue to use the product. And the third is that patient adherence to directions would be crucial to product effectiveness.

The second thing I mentioned is called a communication plan. As I said, this is for healthcare providers. And a communication plan provides FDA-approved materials that are used to aid the sponsor's implementation of REMS, and/or inform healthcare providers about serious risk. And you're probably familiar with the "Dear Healthcare Professional" letters that you may have received about products.

These and other educational materials have been required in the past to alert prescribers to

serious risks associated with the use of certain drugs and biologics. But frankly, we don't know what the impact is of such letters.

The last thing that I mentioned as a component of REMS is something called Elements to Assure Safe Use. And there are six main categories of these elements, and I want to just note, because the sponsor had used the word "mandatory," but mandatory on this slide means, as I said on the previous slide, that the FDA would require and enforce, so that's the meaning of mandatory on these slides.

So the six items here are mandatory prescriber training or certification, mandatory certification of dispensers, drug administration restricted to certain healthcare settings -- for example, a hospital or an infusion center or whatever -- mandatory documentation of safe use prior to dispensing, mandatory monitoring of patients, and mandatory enrollments of patients in a registry.

As you can see from that list, Elements to Assure Safe Use are the three kinds of REMS that I talked about would provide the most strict control

over whether the product is used as per FDA-approved labeling. The downside is that these Elements to Assure Safe Use can impose significant burdens on the healthcare system and reduce patient access to treatment.

Therefore, Elements to Assure Safe Use should only be used if the product would otherwise not be approved due to specific serious risks listed in the labeling.

And in fact, the statute requires -- this is the wording out of the statute -- requires that Elements to Assure Safe Use must be commensurate with specific serious risks listed in the labeling. It cannot be unduly burdensome on patient access to the product and to the -- and they have to minimize the burden on the healthcare delivery system to the extent practicable, conform with elements for other drugs with similar serious risks, and be designed for compatibility with established distribution, procurement and dispensing systems for drugs.

So in summary, FDA does have the authority to require REMS if additional measures -- in this

case, required training -- are necessary to assure the benefits of CCH outweigh the risk. However, the risk management for CCH is for all products. It should minimize healthcare system burden and barriers to patient access to the extent possible within the risk mitigation goals.

Thank you.

DR. O'NEIL: Thank you. At this point, we will take some questions from the Committee to the representatives of the FDA. And the first one to raise his hand is Dr. Weisman.

DR. WEISMAN: Thank you, Kathleen.

I don't know whether Eric or Kathryn, which one should respond to this, but I'll just ask the question.

DR. O'NEIL: They're side by side.

DR. WEISMAN: You've pointed out in your presentation that the level of expertise and experience in doing these injections was limited almost exclusively to hand surgeons, and very few internists/rheumatologists were involved. And therefore, your presentation indicates that there was

not enough information to judge whether with this particular specialty or expertise of these clinicians was sufficient to allow the process to go forward safely.

Since we've heard from the sponsor that their process for screening individuals consists of filling out a form, and that form states just what your specialty is, and that includes rheumatologists, there's no scrutiny further as to additional expertise and then those people would automatically be allowed to use the -- to be able to use the procedure. Is there sufficient concern that you have that given the safety and the risk associated with this drug, that going forward, that this should be limited to hand surgeons as defined -- and we can ask for a moment what the definition of a hand surgeon is -- only and not opened up to generalists, internists or rheumatologists?

Just given the information we have so far on the safety and risk of this drug, is that what your concern is? And I'm trying to understand this.

DR. OKADA: That really is sort of the crux

of the issue that we're asking the Committee to advise us on, is just that we have these very nice study results and they're very -- and they're limited in terms of the background and the investigators. So how do we bring that forward to clinical practice? That's what we'd like you to comment on.

DR. WEISMAN: So that's sort of the crux of the matter here?

DR. OKADA: Uh-huh.

DR. O'NEIL: For the record, those comments were from Dr. Sarah Okada.

DR. WEISMAN: The other side of the question is, can we get a definition from our colleagues on the panel as to what constitutes a hand surgeon? I know from long experience and having distinguished over the years colleagues, associates of mine like Rich Gelberman and Dick Braun and Myles Cohen, I know what a hand surgeon is. But can you define for us what level of training and certification goes along with a hand surgeon, someone that might be, for instance, privileged at our institution to be able to do this procedure or similar procedures on Dupuytren's

patients?

DR. O'NEIL: I will recognize Dr. Kaplan for this.

DR. S. KAPLAN: Membership in the American Society for Surgery of the Hand requires that an individual be board-certified in either plastic surgery, general surgery or orthopedic surgery,and then has done a one-year fellowship in hand surgery. I think that's the current definition. Twenty years ago, there were many routes without certifying bodies, and there is no individual board certification in hand surgery. But there is something called a certificate of added qualification, which is administered by the boards of general surgery, orthopedic surgery and plastic surgery, which requires that one-year fellowship in hand surgery.

So I think that would be a definition, but I'd also like just comment, the procedure of needle aponeurotomy was developed by rheumatologists -- or popularized by rheumatologists in France. So I'm not sure we can -- we should exclude rheumatologists as a whole in this conversation.

DR. O'NEIL: The next question is from Dr. Saag.

DR. SAAG: I, like Dr. Weisman, share the concern that certain types of providers may have less experience. That's not to say that having a label as a hand surgeon or rheumatologist makes you distinctly qualified or unqualified to do this. But I do believe that a certain level of training and acquiring certain sufficient knowledge and skills is necessary to safely perform a procedure that has some risk.

And I want to ask the FDA about the specific mechanisms and perhaps examples about what might constitute mandatory prescriber training or certification. And beyond saying that it's mandatory, is there a way to assure that the training and certification leads to some measurable gain in knowledge or skills?

DR. O'CONNELL: That's a very good question. There are, as you know, REMS out there that have been approved that include the physician attestation or the healthcare provider attestation that they have the training needed to either understand the indication or

use the drug. I'm not really aware of any that actually measures that, like gives a test or they have to go to a hospital and show that they know how to do the procedure. I'm not sure. I'm not aware of any example like that. It's not to say that we couldn't try to design something like that, but right off the top of my head, I can't imagine what that would be.

DR. SAAG: For certain surgical procedures and devices, has the FDA required a practical training experience as part of the mandatory requirement?

DR. O'CONNELL: You mean for use of devices?

DR. SAAG: Say a new surgical procedure or device, yes.

DR. O'CONNELL: I'm not aware of any. Are you?

DR. RAPPAPORT: Unfortunately, we don't have anybody from that center. Those products are located in a separate center, and we don't regulate surgical procedures. So devices being in a separate center, I don't think there's anybody here who would know about that, but we can try to get that information for you.

DR. O'NEIL: Dr. Swartz is next.

DR. SWARTZ: I'd like to address the question of who are hand surgeons a little bit more broadly. I sit as the director of the American Board of Plastic Surgery, and have for the past six years been on the committee for training and certifying hand surgeons in this country. The American Board of Plastic Surgery and the American Board of Orthopedic Surgery and the American Board of General Surgery all have agreed that specific training in hand surgery and certification should follow the plan that was just described by Dr. Kaplan.

However, the facts of the matter on the ground are that there are many, many people who do hand surgery who are not board-certified or certificate of added qualifications in hand surgery physicians. And I'm not aware of very many hospitals that require that certificate to take hand call. If that were the case, we would have a woeful dearth of people able to treat hand patients on an emergency basis.

And for that reason, we don't have as a requirement, at least in our hospital in Pittsburgh,

that you be certified in hand surgery to treat hand patients. You do need to have a certificate in general surgery or orthopedic surgery or plastic surgery and have experience with hand patients and demonstrate that experience in order to be accepted by the hospital for your privileges.

So this really comes down to privileging in a hospital setting for a surgical procedure, and in an outpatient clinical setting, there is no regulation. There is absolutely no regulation in this United States for the treatment of patients in an outpatient setting other than a surgical center facility, and that has to be kept in mind when we talk about who's going to treat these patients and what the risk/benefit ratio is.

My own personal opinion about this is that anyone who has experience treating hand patients and treats them regularly should be allowed to use this medication, and probably will use this medication. And a perfect example of that would be a rural physician, in the old style of the old general surgeon who sees all comers for all kinds of problems. He'll

have the maturity and ability to decide about his risk profile and either will or won't use it based on that. And I think that's where this is going to come down to.

DR. O'NEIL: Dr. Haque has the next question.

DR. HAQUE: I'd like to second a lot of what Dr. Swartz said. The only thing in addition to what Dr. Kaplan was saying about actual certification for hand surgery is that it also requires submission of a case list with a broad base of experience in the prior year to taking an exam for certification that shows that you have experience in several different types of hand surgery, including tendon surgery, bone and joint or fracture surgery, microsurgery or perhaps congenital hand surgery.

So again, everybody's experience level is different, even within hand surgery, and I think what Dr. Swartz is saying is appropriate. I do think that a person who does several injections a month for trigger fingers would have the dexterity and the feel for how to give this injection, and I don't think that

we should necessarily exclude them based on some labeling that -- with their training or background.

The other point regarding devices, I don't know if it's FDA-mandated, but I have had experience with several devices, if I'm allowed to say, endoscopic carpal tunnel release and certain types of implant placements for joint replacements in the fingers where prior to getting approval to do it by the company, I actually had to do a hands-on course where I did cadaver training and listened to several lectures. Did not have a test, but actually had to perform the procedure and people were watching it.

I think that's obviously a huge additional burden on the provider and the company that's marketing the product, but in addition in this situation, it's a little bit hard to do. You can't exactly get cadavers that have lots of Dupuytren's and go in there and practice that. So actually getting a hands-on feel for this is going to be an on-the-job situation.

DR. O'NEIL: Dr. Buckley.

DR. BUCKLEY: I think what we're trying to

get a picture of here is what's the need in terms of patient need and what are our provider resources. So we want to make sure that the most experienced providers deliver this care, but on the other hand, we want to make sure that patients have access to the care. And I think that's where the dilemma is. We're calling it an orphan disease, which makes me think we don't really need to have a huge broad array of providers, although there will always be that patient in some remote area who might not have access.

It sounds like part of the answer might be that's it's providers who do a lot of hand work who have a lot of experience with this, so that we wouldn't want a provider who does an injection about once a year to be doing this kind of procedure. And that might be something else to take into consideration.

I think something we can't forget, I don't know what the reimbursement for this procedure is going to be. But I think we do know in clinical office-based practice that sometimes there's a bias to doing procedures by practitioners if the reimbursement

is high. And so that can lead to practitioners who maybe don't have a lot of experience doing the procedure maybe deciding this is something they should try to get more experience with or do more of. I think we have to be aware of that, that there might be some abuse of this procedure by people who not as experienced.

So it sounds like the challenge is what's the definition of an experienced person giving more-invasive hand care if not surgical care, but I think we have to be sensitive to the fact that there needs to be some restriction on this. And probably that shouldn't be up to the practitioner.

DR. O'NEIL: Dr. McAlindon.

DR. McALINDON: Thank you. I'm trying to put the risk of tendon rupture into clinical context. Given that rheumatologists as well as hand surgeons inject complex small structures in hands and wrists rather regularly, I'm wondering if the FDA in their research found data to look at the overall risk, for example, of tendon rupture following peritendon corticosteroid injection, which is something we do

daily, and perhaps look to see if there are differences between rheumatologists and hand surgeons.

And the second part of this question, I'm wondering -- and the data from the clinical that show I realize are rather small in terms of that adverse event -- whether there was any signal, in fact, that the performer of the injection interacted with the level of risk. In other words, was there something about who did the injection that somehow mediated part of the risk or not? It's a two-part question.

DR. OKADA: This is Sarah Okada. In terms of your first question, we didn't actually perform a literature search to see what the going rate of tendon ruptures with peritendon steroid injections would be, but that's a useful suggestion and we'll take that back.

In terms of the details of who injected the patients who experienced the tendon ruptures, I believe -- and Eric, you can correct me if I'm wrong, but I believe that all of them, in fact, were injected by hand surgeons, which is sort of consistent with the fact that there were mostly hand surgeons doing the

procedures.

DR. O'NEIL: I'd like to ask a simple question, and this probably goes more to the sponsor. I know that's not quite right, but it's pertinent to the discussion at hand, which is was there any evidence that any of the different proposed methods of education had a bearing on either the success of the procedure or the ability to avoid complications?

DR. DELCONTE: We were not able to do the type of training that the investigator or sub-investigator had performed and the outcome, that just wasn't possible from the way we collected the data.

DR. TURSI: Just one comment, what I can also do, though, is provide a little context in regards to comparison of what the investigator training looked like versus what we're proposing, with your permission.

What I've done with this particular slide is I've kind of put side-by-side the injection training of the investigator versus the proposed physician training. And what ultimately we're proposing, we

believe is actually not only improved the investigator training, but includes additional facets to that training. When we consider the first area of training, which is the preparation of injection technique and finger extension, naturally, that was included as part of the investigator training. But we've gone ahead and improved that, and I can get into detail, should you desire, as opposed to going through the other points.

In terms of adverse event reporting, clearly, that would have been included as either part of the investigator brochure or part of the study protocols. But we've actually now encapsulated all that information in one structure, and that being the proposed training program. So physicians don't need to go to multiple places to get that information. They've got it all at their fingertips in one resource.

As it relates to important safety information and adverse event descriptions, again, we've gone beyond what we did in the investigator training. Other areas that weren't included in a

specific investigator training -- injection training specific to the joint, the risk of tendon damage, frequently asked questions, self-assessment, sequential completing of training being required prior to attestation and attestation being required before use -- they are all new additions to our proposed training program.

So I appreciate the opportunity to add that. Thank you.

DR. O'NEIL: Dr. Weisman, you have a question.

DR. WEISMAN: Yes, I want to -- question back to the FDA, though. I agree with Lenore. I think we need to focus and get away from this sort of food chain issue discussion, and talk about what really is the crux of the matter here, which is the discrepancy between what was done in the clinical trial and what's being proposed for safety monitoring and safety assurance in what the sponsor has given us. And now there's another discrepancy. The sponsor has now told us that they actually have improved upon that imbalance, and they're better when the way it was when

they had the -- during the study and now the FDA has reviewed this and said that there are some gaps between what the sponsor is proposing and what had actually gone on during the trial.

Let's focus again on those gaps and your interpretation of what the sponsor had just pointed out, that they've improved upon this. Have they actually improved this or do the gaps still remain between what was done in the trials and what's being proposed going forward for the use of this procedure?

And this is not just an injection. This is not somebody getting an injection into a de Quervain's tendon. This is a procedure where it involves manipulation following the injection and a recognition that a tendon might have ruptured or that a ligament was ruptured following the procedure, which requires some definite cerebral expertise in being able to sort that out postoperatively or postinjection.

So it's not just an injection. I think we need to keep that in mind as well.

DR. OKADA: This is Sarah Okada. So we did have an opportunity to review the revised training

manual and DVD that's proposed for use in clinical practice, and we actually concur with the sponsor that they've made some significant improvements in these things. And so they're fairly comprehensive.

The situation obviously is still somewhat questionable in terms of how much sort of hands-on and person-to-person training went on during the trials versus what would be the case during clinical practice. That's not so clear. Obviously, they're proposing to have some liaisons available. We're not completely sure what the background of those liaisons would be, whether they'd be available for any clinician who wanted to inject it and needed some hands-on assistance. Those details were not -- haven't been finalized, so we're not clear on.

DR. RAPPAPORT: Ultimately, we're going to turn it back to you, Dr. Weisman, because it's really the questions that we're asking you today is based on the information we have, which is everything you've seen. We're not hiding anything. What do you think about whether the training is adequate, whether you think that the practitioners need to be from certain

groups or have a history?

All of those questions are what we're asking you, because there's no simple answer here and there's no way to study that without another ten years of extensive clinical trials that I'm not sure can even be done. In the meantime, we've got patients who may benefit from this.

DR. O'NEIL: Dr. Saag.

DR. SAAG: I think Dr. Rappaport and Okada are circling around the question that I asked earlier, and it may be that we're in a bit of somewhat uncharted territory with these risk management plans. But I think what would really help the panel out is to have a little more guidance from the FDA about what are the possibilities. Certainly, what the sponsors are proposing is reasonable. It's necessary, but is it sufficient? Is it enough?

We know from adult learning theory and other approaches to trying to train practitioners that you can increase knowledge but you may not change practice. You may not actually improve skills. So is this sufficient? It's necessary, but is it

sufficient? And understanding better what in this sort of new model that the FDA has adopted to more extensive risk management plans, knowing what other things are available in the armamentarium that the FDA could require would be very helpful to the panel.

DR. RAPPAPORT: I hear two questions in there. One is what can we do under our REMS, and the other maybe what is needed, or do we fully understand what's going to work in this situation and how we're going to assess that.

So with the second question, I'm not sure we have an answer to that yet, that we really don't know a lot yet about how REMS work. There's a lot of history of education, patient education, physician education. There are experts at the table here who can tell you more about it that we can probably.

But as to whether we should be imposing the restrictions that Kathy went over with you, and that's the limit of our restrictions. We can require that only certain prescribers, specialties, are actually doing these procedures or we can do nothing. Those are the extremes.

Let’s go back to the fact that we have over the last couple of years since we’ve had this authority learned some new things about imposing restrictions, and you need to take the impact of imposing restrictions into consideration in whether we should really be doing that.

The company has already provided quite a restrictive plan, and whether it’s going to work is yet to be seen. And, perhaps, what one possibility is to let them take the responsibility at this point for making sure that the right people are receiving or are being allowed to use the product. And then we can monitor over time and see how that’s working. That’s one option.

The other option is that we could step in and do our own mandated restrictions that have the authority of law and that we could fine people for not doing. If we do that, however, we’re imposing a huge burden, and that’s part of what was in that law, as Kathy explained to you, that we’re not -- we have to consider how much of a burden we’re placing on the healthcare system. There’s a huge burden and a huge

price for every restriction that's put on any kind of medication.

If you think about what's out there, what's approved for use, there isn't any medication out there that doesn't have significant risks. Drugs are unsafe, and you have to consider what -- how far you want to go in having the federal government actually be the restricting agent. If this doesn't work, we can always step in later. If we see increasing problems with tendon rupture over time that are at a greater incidence than in surgeries or other new problems, we then still have the authority to step in and provide additional restrictions.

Did that answer your question at all?

DR. SAAG: It's helpful. Thank you.

DR. O'NEIL: Dr. Buckley.

DR. BUCKLEY: I guess two comments. One is that the company's provided a certain bar to get access to performing this in terms of your background training, but they really haven't talked about the volume issue, how many procedures do you need to perform a year, so that certain -- probably hand

surgeons are by definition doing that quite a lot, but rheumatologists might be performing one procedure a year or one procedure every two years. And if you believe it's not just your training but continued practice, and I think for most practitioners, it's probably continued practice where they learn 80 percent of what they know. The training is 20 percent. It's doing it over and over again is the other 80 percent. So we may be missing that in what they're offering us.

The other thing I have a little bit of concern about is, you weigh risk and benefit is a little bit of the benefit issue, because when we talked about that, we talked -- if you look at Slide 10, where we talk about the success of getting to the primary endpoint by kind of training, one of the things that struck me was that although there wasn't a difference by the types of physician training, there was a big difference in success rate between Study 57 and Study 59.

This was a placebo trial, but I imagine given that almost all the patients got adverse

reactions, neither the patient nor the physician was blinded for very long. I suspect that these measurements were made by the physician who did them, not an independent monitor or a picture taken.

So these results in the first study, 57, the good response rate was 60 to 70 percent. In 59, it was 40 to 47 percent. In the real world, maybe among people who are a little less experienced in this, the results may be less. So we have a procedure that no one denies probably is going to be very helpful to some people, and we have some risks that we don't quite understand. And when we put those things together, I think there's still some concern.

DR. DELCONTE: Dr. O'Neil, would I be able to address the issue of the differences between the studies, perhaps to shed some light on that?

DR. O'NEIL: If you can do it in under a minute. We're running a bit late already, and we have three more questions.

DR. DELCONTE: The difference can be explained by the difference in the severity, and I had shown earlier that the MP joints of low severity

performed better than the high severity. In Study 857, most of the joints were MP of low severity. In the second study, in the Australian study, there was a predominance of PIP of greater severity, so that could account for some of the differences.

DR. O'NEIL: Thank you.

Dr. McAlindon.

DR. McALINDON: Thank you. So I'm just a little concerned about what I perceive to be a slight logic gap, in that we have great concern about the incidence of tendon rupture, and we're responding to it through restriction of access to individuals who have skill in hand surgery. But I think the numbers are too small in terms of that adverse event to really inform us one way or another whether any part of that risk was mediated by skill level. Indeed, the ruptures occurred among physicians who were presumably quite skilled at performing hand injections.

So it could be that the risk is mainly mediated by patient and disease characteristics rather than the skill level. In other words, it may be sufficient just to put the intervention in the right

place, and the rest of the consequences are then dictated by the patient characteristics.

So if that's the case and this is hypothetical, if that's the case, trying to mitigate that risk by a complex program that either restricts access or educates physicians might not in fact have much impact on the incidence of that outcome. And I think we just need to understand it better in order to figure out how to reduce that.

DR. SAAG: Can I respond to that?

DR. O'NEIL: Sure.

DR. SAAG: Tim, I agree with your premise, but I'm not sure that the clinical trials address the issue. I think there's a problem, that of generalizability; namely, all of the people performing the clinical trials were skilled. But what we don't know is what happens when we get out into the real world and we have people that spent 20 minutes watching a video doing this procedure who aren't familiar with the hand anatomy properly?

And knowing that there is the potential for a risk and that the risk has been seen in the clinical

trial, whether it's related to the patient characteristics or to the injection technique is not known, but one could easily speculate that if there is a component of injection technique that is in some way responsible for some proportion of adverse outcomes, that this would be manifest and magnified considerably greater in a real world setting than in a very controlled clinical trial.

DR. O'NEIL: Ms. Aronson.

MS. ARONSON: I have, I think, a quick point of clarification. I'm trying to understand what might fall under REMS. If there was some kind of guidance that if a patient presented as complicated; in other words, if the patient also had rheumatoid arthritis and some deformity, then it might be advisable for the patient to be referred to someone with high experience in hand issues. Would that fall under the REMS or, would that be just some guidance that could be put out?

DR. OKADA: This is Sarah Okada. I'm not really familiar with any REMS that gets down to that level of detail in terms of trying to dictate sort of

clinical practice. However, if it were really important and we thought that that would mitigate a specific risk, I could envision that some component of a REMS could be constructed to address that. I'm not certain that that's going to be the case here, though.

DR. RAPPAPORT: And it doesn't have to be as part of a REMS, either. It could be part of the program that the company is providing without us intervening.

DR. O'NEIL: We have time for one more question, and Dr. Haque has a question.

DR. HAQUE: I just have one question for Dr. Rappaport, and that's rather than go in the full-blown REMS with the cost and other issues that you mentioned earlier, can we -- are we in a position to make some suggestions that at least a registry be maintained so that we can quickly catch a trend if we see one rather than just have these patients get their doctors certified, they get their injection, they get one follow-up maybe, if that and then they're lost afterwards?

DR. RAPPAPORT: There's a whole range of

possibilities here, and we are very interested in what your thinking is on those, and we'll certainly take that into consideration in where we end up with this.

DR. O'NEIL: Well, I'd like to thank everyone for a lively and interesting discussion which we will be able to continue somewhat later in the program. We will now break for lunch, and we'll reconvene again in this room in 45 minutes, at 12:45. Please take any personal belongings you may want to with you at this time, and Committee members, please remember, again, that there should be no discussion of the meeting during the lunch among yourselves, with the press or with any member of the audience.

Thank you.

(Whereupon, at 11:57 a.m., a lunch recess was taken.)

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

DR. O'NEIL: Thank you, and welcome back to the meeting of the Arthritis Advisory Committee. We are about to begin the open public hearing, and before I do that, Nicole Vesely has some comments.

DR. VESELY: 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, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing 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, the 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.

The FDA and this Committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this Committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the Chair.

Thank you for your cooperation.

DR. O'NEIL: We will begin with comments from Mr. Tom Fewell. Mr. Fewell.

MR. FEWELL: Thank you for the opportunity to come here today to tell you about a treatment that changed and restored my life. My name is Tom Fewell.

I'm from Sycamore, Illinois. I was first diagnosed with Dupuytren's contracture in 1997, and have lived and adapted to the effects and limitations of this disease since then. Between my right and left hands, I've had two surgeries, and I've also participated in the AA4500 clinical trial in '07 and '08.

I received minimal compensation for mileage during the trial from Auxilium. I also participated in an advisory board meeting in November of '08, and Auxilium arranged and paid for the travel and lodging for that meeting. They also arranged for the travel and lodging so I could attend this meeting today. I do not own any stock in Auxilium.

Previous to my diagnosis in '97, I steadily lost function in my left hand. That affected my productivity at work, especially keyboarding and picking up objects. I also could not participate in recreational activities like playing ball with my kids or playing golf.

My first surgery was an outpatient procedure, and it was effective. But within months, more cords started to form on the ring finger of my

left hand, and I had surgery again on my left hand in 2001. The second procedure was much more extensive and invasive to my nerves and skin. Anesthesia was used during the procedure, with its inherent risks. I lost time and productivity from my job during this time because of the follow-up appointments and six to eight weeks of rehab it took to regain my strength and flexibility.

So the surgery was more effective and long-lasting, but was also significantly more risky, painful and expensive.

As more cords started to form, this time in my right hand, I put off and delayed more surgery because of the pain, risk and expense until the contracture seriously interfered with my daily activities and ability to perform my job, as well as limited my personal life and mental outlook. Again, I lost productivity at work because of the difficulty and frequent mistakes in using a keyboard.

During my working career, I was a senior buyer, an international business buyer, and met business leaders through Asia, Europe as well as the

U.S. and Canada. Making a good impression is important, and that starts with a confident, firm handshake. As my hand contracted, I felt less confident and sometimes embarrassed because of my strange handshake.

Gardening was also difficult and painful. My hands tired easily when I played golf. Putting on gloves became a five- to 10-minute ordeal because I could not open my palm to insert my hand into the gloves, even mittens.

When I finally made the appointment to discuss surgery again in 2007, Dr. Beher (?) told me about an upcoming clinical trial using injections and outpatient type of procedures rather than surgery. I was in a unique position to be able to compare and contrast the effectivity and risk of injections versus surgery. Two surgeries, one set of injections, it was an easy choice.

I participated in the trial. During the treatments, I did feel very sharp pains during the 10-second cycles when the doctor physically straightened my hand, breaking the cord tissues apart.

I managed coping with those intense cycles because I knew and expected that when the cord tore apart, I would experience immediate and significant improvement in my hand movement, range and flexibility. And after three cycles, I recovered full use of my hand.

I engage in all activities I want to, recreational, keyboarding, the many things you take for granted, and putting your hands in your pockets to get keys, I could do that again. And I could shake hands, and I could clap when my kids did something well, something I couldn't do before.

The collagenase treatments eliminate the risk and uncertain results of surgery. The treatments resulted in immediate and effective improvement in hand motion and quality of life. There is some pain, but it is manageable, especially considering the extensive rehab that is also eliminated. And although longevity is still being studied, my treatments ended 18 months ago and the cord has not reappeared. I think the injection treatment represent a win-win scenario for reducing pain and improving the quality of life and reducing patient risk.

Thank you.

DR. O'NEIL: Thank you, Mr. Fewell.

The next speaker will be Rodney Van Sickle. Mr. Van Sickle.

MR. VAN SICKLE: Hi, my name is Rod Van Sickle, and I've had Dupuytren's for about 12 years. I do not own stock in Auxilium, and I've received only minimal compensation for my time and travel.

Dupuytren's affected my right hand first. I tried to postpone it because the doctor told me at that time that there was a drug going to become available, but I couldn't wait any longer. I couldn't perform my job as a fire captain any longer, so I went ahead and had the surgery.

After the first surgery, I got a staph infection, and that required me to have a second surgery. And the disease came back with a vengeance in my little finger in my right hand, completely closed against the palm of my hand, and I had to have a third surgery. The little finger on my right hand now is at about 90. This is as good as it gets.

When the trial became available and I was

allowed to be in the trial, and after the three injections -- before that, the ring finger on my left hand was at about 50 degrees. After the three injections into the cord on that hand, the cord popped after the third injection, and my left hand is perfectly straight.

And if you compare the -- there is no comparison between -- in my opinion, between the surgery and the drug injections. It's just -- I had such a horrible time with the surgery, nothing against the surgeons, but it just didn't work well for me.

The disease runs in my family. My father has it. My brother has it, and my two sons have it to different degrees. And I would really like to urge you guys to approve this drug for the market because it would help so many people. Thank you.

DR. O'NEIL: Thank you.

The next speaker is Ms. Karen Mercaldo.

MS. MERCALDO: My name is Karen Mercaldo. I'm 61 years old. I do not own stock in Auxilium, and I've not been compensated except for my travel expenses.

I was diagnosed with Dupuytren's disease in 1996 during surgery for what the doctors thought was a cyst. I was 47 years old at the time, and I knew what Dupuytren's was because my father has had it ever since I can remember. He had two unsuccessful surgeries in the ‘50s, and as a child, I remember hearing him say that he would cut his hand off before he ever went through that again.

My recovery from surgery was long and difficult. For the first week, I had to wear a sling that positioned my hand directly in front of my face. For months, I kept dropping things and sometimes burning myself because it took that long to get the feeling back in my hand.

Within two years, the problem returned on the same finger and two others. It was much worse than before, and on both hands. I was discouraged. It didn’t seem worth going through the surgery if the condition was going to return. Three of my fingers were affected at the PIP joint so that my hands looked like this.

Everything I did became more difficult.

Simple things like putting on a glove or typing were cumbersome. I managed to adjust in many ways, but had to give up completely things that had enriched my life, such as playing the piano, knitting and painting. I couldn’t even wear my wedding ring.

Then one night a friend of mine who also has Dupuytren's showed me his pinky, which was almost completely straight. He said to me, “Yesterday, it was like this.”

He told me that he was a patient in the clinical trial, and I didn’t need any convincing to find my way there. I had my injections in August, October and November of 2003. The morning after the first injection, the doctor took my finger and straightened it. It hurt momentarily, but the tears in my eyes were tears of joy. I was thrilled. I found that although there was some soreness, I could use my hand immediately. I did some exercises and wore a splint at night. I anxiously awaited the subsequent injections and was just as pleased with the results.

Now, six years later, I still have the full

use of both of my hands. I enjoy playing the piano. I've started a knitting club for my granddaughter and her friends. I never poke myself in the eye while washing my face anymore, and I'm wearing my wedding ring. I even started playing the viola again after many years, something I thought I would have the dexterity to do. I enjoy it immensely, and I play in church every week.

My Dupuytren's symptoms have not returned, but more significant to me is that my fear of the symptoms returning, which was very great, is gone. Most people never think about the blessing it is to have the use of their hands, but I think about it every single day, and every day, I'm thankful. I have a son who is a gifted pianist, and grandchildren who show promise in music and art. It is for my children and grandchildren and not just for myself that I appeal to you to approve the drug Xiaflex. It would mean so much to me, to my family and to the many others who suffer from this debilitating condition.

Thank you.

DR. O'NEIL: Thank you, Ms. Mercado.

The next speaker is Kenneth Nelson.

MR. NELSON: Good afternoon. Madam Chairman, thank you, and the Committee, for your time today and for the opportunity to share my experience as both a victim of Dupuytren's contracture and as a beneficiary of medical research that is the subject of today's hearing. My testimony is mine and mine alone. I do not own any stock in Auxilium Pharmaceuticals. I have not been paid anything for my appearance today other than for travel, lodging and meals, and a small stipend for my participation in the clinical trials.

I have no other motive for being here today other than to voluntarily share how this exciting has returned a quality of life I really enjoyed but I lost more than 20 years ago. I first became aware that something was wrong in my early 30s. I noticed some lumps developing in a pit in the palm of my left hand. By my early 40s, these things appeared in both hands. It felt like a cord or lumps just under the skin. There was no pain. I had no restrictions of movement in my fingers or thumbs, but it was something that I brought to the attention of my family physician.

Well, since I did a lot of physical work around the house, he passed those lumps off as calluses and we left it at that.

But a few years later, I noticed that my third and fourth, or ring and small fingers and thumbs, were slowly beginning to contract. By age 45, the condition was beginning to prevent me from doing things that I loved to do like playing the piano, or as it’s even been said here, washing my hair without poking myself in the eye, or even trying to put on a pair of gloves or shaking hands with clients.

My doctor then finally referred me to the Indiana Hand Center. The diagnosis was Dupuytren's contracture. I had not a clue what that meant. I was told the condition would only worsen, that the only option at that time was radical surgery. I was shocked to see the extent to which my hands had to be cut or sliced open to remove the growth, followed by a boxing glove-type wrap and lengthy rehabilitation to regain movement and strength. There was also the possibility that I could lose some of the feelings in my fingers. There was the threat of potential

infection and that Dupuytren's was likely to return.

Radical surgery was not an option that I was willing to accept at that time. At least I could still hunt and peck on the computer keyboard. I even found sort of a simple way to play Chopsticks on the piano again. But this continued to worsen and seriously affected my quality of life. Even when shaking hands with people, they would often ask me, Ken, have you been the victim of a stroke -- were embarrassed to ask you. I would jokingly tell them as I held their hand that I had a highly contagious disease and they would withdraw very quickly, but I tried to find some humor in these conditions.

I remained hopeful that medical science would develop a safe, noninvasive procedure that would give me back the use of my hands without having to go under the knife. Well, that day came when my wife Susie read a notice in the newspaper seeking candidates for a clinical trial designed to reverse the devastating impact of Dupuytren's. After undergoing a medical exam and extensive questioning, I qualified as a candidate.

Dr. Kaplan, who is here, of the Indiana Hand Center, was very thorough in explaining the process followed by the cord rupture procedure. He made sure I understood the process, beginning with the need for blood chemistry. My first injection was uncomfortable but tolerable. Attempts to rupture the cord proved futile and painless. I was among the group to get the placebo.

Well, eventually, I received the real thing. Once again, the injection was uncomfortable, this time with an increased stinging sensation. My fingers were immobilized with a wrap, and I was sent home. Later that day, I accidentally bumped my fingers. I felt something like a wasp or bee sting in the palm of my hand. I already could begin to hear this cord rupturing or popping. I could feel it. Well, upon going to bed that night, I removed the wrap as instructed and noticed a slight bruising in the area of the injection. I was very careful not to extend my fingers or intentionally try and rupture the cord, although it was tempting.

The next morning, I returned to the hand

center. Because of the trial requirements, numbing medication was not administered, and Dr. Kaplan explained there would be a rather sharp pain when and if the cord ruptured. But it would last only a moment. He was right. As Karen has said, when I heard that cord pop and saw my fingers suddenly straighten out after years of being jammed into the palm of my hand, tears came to my eyes. I get emotional about this still.

It was partly because of the moment of pain but mostly due to the emotion of witnessing what I still call a miracle in my life. Well, at the end of each rupture session, I was fitted with a night brace to help keep my fingers from retreating back into the palm of my hand.

I can just simply sum up my remarks by saying that I inherited this from my dad who has Dupuytren's. Our youngest son Bradley is beginning to get the pits and the cords in the palm of his hand. It’s worked for me. It’s been a wonderful procedure. I thank Dr. Kaplan for his professionalism. And I highly encourage you to go ahead and proceed

with this and give it an okay.

Thank you.

DR. O'NEIL: Thank you.

The next speaker is Bill Walker.

Mr. Walker.

MR. WALKER: Hello, ladies and gentlemen. I want to start with the disclaimer that I have no financial affiliation with Auxilium, and I've just been also paid -- not paid but just reimbursed for travel expenses. I'm here today purely out of my enthusiasm for this drug because it changed my life totally. I get emotional, too. I'm sorry.

But like Ken, it started in the 30s. You get a pitting in your hand, and you don't know what it is. And over time, it's very insidious, and it takes maybe eight to 10 years to really where it draws your hand back to -- it's not useless, but it's close to that. I mean, you can drive and you can live, but you can't live like you used to. You can't play tennis. You can't -- again with gloves, I'm a device rep, and I work in the OR in a lot of hospitals. And you can't even put latex gloves on to protect your hands

from -- you know universal precautions. You would have to get a sterile towel and grab a cable that is passed off to you because it has heme from -- it's a surgery thing.

But anyway, being included in the trial, I was on vacation two years ago. We were in Italy, in Tuscany, and my tour guide was from Indianapolis. She was in Dr. Kaplan's trial. She looked at my hand and said, "You have Dupuytren's. You should go to the hand center and see if you can be in this study."

So I met Dr. Kaplan, and he looked at it. I was fortunate enough to be randomized to the real deal. We had the collagenase enzyme. The first injection, that night at home watching TV, my hand starts to pop open just spontaneously with the boxing glove dressing on, and it was nothing short of miraculous. And I go back in and see Dr. Kaplan the next day. My hand was very affected. It was 70 degrees back to -- these two fingers on the right hand. Within the -- after the first month, you go back and you get another round of injection. It was virtually straight at that time, one month and the

hand’s almost normal.

I had seen one of his colleagues maybe a year prior to that, and like Ken was saying, he saw the surgery and it’s a lot. It’s very scary to have to think about the surgery. I work probably 70 hours a week, and I don’t have time for surgery. I don’t have time for physical rehab because I’m very devoted to my job.

But anyway, being included in this study has really changed my life. And if you also look at if you go to surgery, the anesthesia risk, too. That’s a big risk, the risk of infection, which you heard Rod say he had that happen, too. And with the enzyme injection, they target -- Dr. Kaplan was really -- well, he’s an expert. He can look at the cord, a very fine needle penetrates into the tissue, three injections, 0.58 milligrams and it -- being an enzyme, it just dissolves the tissue and allows the hand to break open.

Now, if you compare that to a surgical approach, it’s just -- the surgical approach is a totally different animal, and the benefit from the

injection I think just outweighs by far a surgical approach.

And the things about -- I drive sometimes 240 miles a day. I would get -- I would see him in the office at 7:00 a.m. I could be in the OR by 10:00 in the morning at Madison, Indiana and be performing my work. Even with a dressing on my hand, you can still work around that, and the dressing is only on for 24 hours. But I lost no time at work, and I had a perfect result.

This hand was 70-plus degrees back. It's straight as an arrow now. It's been that way for a year. And at Christmastime, you get gifts like gloves, my mother, she'll get you gloves, and I could never wear them. When she saw my hand, she had tears of joy. She was so happy. And it's just -- I'm really privileged to be part of the program here. And I just want to thank the hand center and Dr. Kaplan.

And you folks in the FDA, we need this out in the streets as soon as we can, so I'm a total believer in it and a recipient as well. And I just want to thank you all.

DR. O'NEIL: Thank you, Mr. Walker.

We will now have very brief comments from Dr. Robert Hamilton, a Ph.D. immunologist from Johns Hopkins.

DR. HAMILTON: Thank you, Panel.

First, I own no stock in Auxilium, and I have no vested interest in the drug itself one way or the other. I'm here today because my clinical laboratory at Johns Hopkins did the initial immunogenicity studies on the Phase 1, Phase 2 and early Phase 3 studies of Dupuytren's that were done at Stony Brook back from 2001 to 2006.

And as you who are medically qualified know, there are five classes of immunoglobulin or antibodies, and of those, IGE drives allergic disease and IGG is viewed more as protective. So one of my puzzles was not to see the breakdown of the immune responses in the Phase 3 study into IGE and IGG.

So in our initial testing with the Dupuytren's sera from Stony Brook, what I can say is that we detected IGE antibody to collagenase in approximately a third of the individuals who were

subjected to the analysis or to the studies. After repetitive injections, some of these levels arrived at levels that we see with patients who have hymenoptera venom allergies and have reactions.

Because this was a primary immune response, you would not expect to see allergic reactions during the first three months of treatment, because the immune response is just beginning. The concentration is low. The affinity is low. The specificity is not what it could be.

And the Phase 3 study clinical data today support the notion that in fact, the first course of treatment of three injections is safe. It doesn't elicit obvious systemic reactions. So up to one to three injections -- based on the data, the clinical data supports the safety of it.

Today, we heard that there was 100 percent of Dupuytren's patients who elicited antibody responses. I'd like to know how many of those elicited IGE, not because in the first course of treatment they would be expected reactions, but if they ever choose to come back for a second course of treatment, that's

precisely where you're going to see the systemic reactions. And I would suggest that if you do license the drug, that you license it for a first course of treatment, and that you request additional studies to document the safety of the drug when patients come back for repetitive administrations four to six months after administration.

Second, that you identify or define what is a large local or a systemic reaction so they know what to look for, and that any individual who manifests those symptoms in fact gets a blood sample and gets at least evaluated from an immunogenicity point of view in terms of IGE and IGG antibody responses that are technically capable -- we're capable of doing those measurements analytically today.

So thank you very much. I only have three minutes. Thanks.

DR. O'NEIL: Thank you.

We had a number of questions left over from the first session, questions to the sponsors from the panel members, and we will begin there with Dr. Kaplan.

DR. S. KAPLAN: Thank you. As a hand surgeon who's dealt with this condition for many years, I welcome a viable alternative to surgery, and this may be such an alternative.

I do have concerns. I share everybody's concern about the crucial nature of the injection, and making sure that the right people who know the condition and understand are involved.

I share Dr. Swartz's concern about off-label use. I know that there are Stage 2 clinical trials underway for use in frozen shoulder and Peyronie's disease. At a recent medical meeting, if you stopped by a booth, you got a candy bar and you can do a survey, and the survey was clearly about this use of this product in other conditions.

Severe scarring being one of them, plantar fasciitis being another. I can envision a variety of conditions where people might want to try this off-label, and I would be worried about that.

I have two very specific questions. One, you mentioned an ongoing study of two- to five-year follow-up. I'm sure you are aware that the results

from Stanford of an eight-year follow-up recently presented at the American Society for Surgery, the hand meeting at San Francisco. They had eight people followed after eight years. Six of the eight had recurrence. In two situations, the recurrence was actually worse than on original presentation. The four others, it was mild and two others, it was -- it did not recur.

And although your two- to five-year studies are not complete, do you have other data on recurrence that you've not shared with us?

My second specific question involves your recommendation for injecting only one cord at a time. You demonstrated product safety. We just heard about some concerns about IGG and IGE. If the recommendation is to inject one cord at a time and you have what in my office is a fairly common situation of bilateral involvement with multiple fingers, it could conceivably be that a person would come over the -- for 24 visits with 12 injections and take a year to do so for treatment of two fingers on each hand.

And my question is then with the safety

profile you outlined, are you going to modify that recommendation? Thank you.

DR. DELCONTE: Let me address the first question first about the recurrence, and then I'll have Dr. Tursi talk about the injection regimen, because there were a number of patients who had various intervals between injections.

What we had talked about was in the durability of response was 830 successful patients treated, we had 30 recurrences. And as you'd heard, the definition of that is a recurrence to a contracture of greater than or equal to 20 degrees with a palpable cord. If you do Kaplan-Meier estimates, the rates at one year are 6.7 percent on the successfully treated joints.

The data we showed from some of the surgical therapies -- and this is the average follow-up of 12 months -- within or lower to that range, about 19 to 22 percent.

Then the last question about the follow-up study, that's an ongoing study which will take the patients from the current clinical trials, and that's

a two- to five-year follow-up. So we'll get some additional long-term recurrence data there.

And that's -- to answer the question about the series of eight patients from San Francisco, we realize that's a small number of patients, and that's the reason why we'd like to do the long-term study.

And then, Jim, you want to come up and address?

DR. TURSI: Sure. Jim Tursi, with Clinical Affairs.

As to the safety of injecting more than one joint at a time, that would not be a recommendation that we have, as it was not studied during the clinical program. If you'd like to see, I can show you some details on subjects that were treated close together in proximity, meaning short inter-injection intervals. But I'll leave that at your discretion, if you'd like to see that.

DR. O'NEIL: If it's informative, I think we would like to see that.

DR. TURSI: Okay. What I've done is I've taken those subjects that have had essentially two

weeks or less between injections. And as you can see, these are the subject number along the left side. And the days between the injections ranges from 10 upwards to 15. Just to explain the organization of the table, at the top is the original joint that was treated, so in this case, it was the left ring PIP joint. And in parentheses, it just demonstrates that it was a success.

The joint below was the one that was ultimately treated at the interval following. So this was treated 13 days later. This particular joint 10 days later.

And what's important to point out was that even in these subjects, first of all, they were all successful with these short intervals. The second important point is to point out that when you consider the adverse event profile, the adverse events that we saw in these subjects was no different than those subjects who had received at a 30-day interval or a longer interval.

DR. O'NEIL: Thank you.

We have at least two other questions for the

sponsor that have been identified to me, but I had promised the sponsor three minutes or so to present additional data. Are you ready to do that?

DR. DELCONTE: I just had one point of clarification on the qualifications and actually the training of our investigators. As we had mentioned before, we selected investigators who were hand surgeons, orthopedic and rheumatologists. And their relative level of experience, we had one sub-investigator who was in their first year out of fellowship, and we had several who had been in practice for more than 20 years.

Regarding the sites, we had not -- in addition to academic medical centers, we had large research clinics as well as private practices. So we tried to get as broad a range of possibility in the sub-investigators with regard to training and type of practice. That's all.

DR. O'NEIL: Thank you.

The next question was from Dr. McAlindon.

DR. McALINDON: It was a quick question in relation to, again, the tendon rupture issue. So I've

been wondering about whether tendon rupture that occurs as a consequence of AA4500 might be more difficult to repair than tendon ruptures that occur in other situations. I'm wondering if we have any data on that, or whether the operative findings perhaps were informative in that respect.

DR. DELCONTE: Yes, I'd like to ask Dr. Kaplan to come up and talk about operative findings on patients who've had AA4500.

DR. T. KAPLAN: There's a number of details in the three patients who had tendon rupture intraoperatively. I unfortunately had the opportunity to see one of them firsthand, as one of the tendon rupture patients was one of my own. That patient, unfortunately, he was also someone who had previously had surgery on his other hand. After that surgery, he experienced a flare reaction, and he was out of work for six months. So he was very interested in the potential for less-invasive treatment.

Unfortunately, with his first injection of Xiaflex given for the PIP joint, it was actually given at the radial base of his small finger. He went back

to work with limited time off and was moving a pallet. So we didn’t -- at that point, he was the first point tendon rupture that had happened. There was no recommendation at that point that I had given him what not to do as far as forcible use of his hand.

He had a heavy pallet to move, was lifting up that heavy pallet with a pallet jack when he felt that tear.

Because of his experience with surgery on his other hand, he was very reticent to undergo a surgical procedure on that hand. So because he had ruptured his FDP tendon but his FDS tendon was intact, we first watched him to see whether or not he would function well with a superficialis finger, meaning that we didn’t expect him to get motion back at his DIP joint, but he could still have functional motion at his PIP joint.

Unfortunately, he didn’t get back the motion that he wanted. He had some discomfort from where the tendon rupture was. And when we explored him, found what we would typically see with probably more like a rheumatoid tendon rupture, where there was an

attritional rupture of that tendon. There were not healthy tendon ends to consider repair to, and the decision was at that point -- I talked to him beforehand about tendon grafting procedures versus just excision of the FDP remnant and a tenolysis of the FDS, which is what we did in his circumstance.

In one of the other tendon ruptures at one of the other sites, they intervened much more quickly, but again, they had to do a tendon reconstruction procedure, excise the damaged tendon and put in a tendon spacer for several months and then went back to do a tendon grafting procedure afterwards.

So I anticipate that when ruptures happen due to collagenase, that it would be a rupture that would not be directly repairable. You'd have to consider reconstructive options.

DR. O'NEIL: Thank you.

Dr. Olsen had a question as well.

DR. OLSEN: I had a question actually that was just touched on in the discussion, which was I wondered what the antibody classes were of the antibodies that the patients made to the drug, not

just IGE, but I was concerned also about classes of IGE that might consume complement and with re-challenge, you might face problems, for example, with immune complex formation.

DR. DELCONTE: Okay. I'll have Paul Chamberlain address that, and I should also mention we did have a number of patients, because of the way the trials were designed, who had a large interval between their double-blind portion and when they went into the open-label portion. So there was in some instances more than six months. And some patients in earlier trials had been exposed up to five years earlier, who'd been in later trials without any untoward effects.

So, Paul.

DR. CHAMBERLAIN: It's Paul Chamberlain, NDA Regulatory Science.

Yes, just to address the assay specifics. We were measuring total antibody. That's AUX-I or AUX-II specific antibody, regardless of class. So that would be substantially IGG, and we probably wouldn't detect specific IGE in the assay, but it

would be measured in the total assay.

I think the issue in terms of the IGE question that Dr. Hamilton asked is best addressed in terms of patients who followed up into Study 858 from 857; that is, they had a series of treatments in one study and then rolled into a second study. And that would be when you most expect to see an exacerbation of the immune-mediated adverse drug events.

And these data show in the top panel the first pivotal study, this was 857, subjects on successive injection showed increasing titers of anti-AUX-I and anti-AUX-II antibodies as you move across from the first to the fifth injection. Subjects then rolled over into a follow-up study, an Open-label Study 858, and you can see at the time of the first injection, the titers were pretty much back down to the baseline level, but then rebounded on the second, third, fourth and fifth injections.

So this is exactly the scenario that Dr. Hamilton would expect to see, an exacerbation of immune-mediated adverse drug events. So I would like to hand over to my colleague Dr. Jim Tursi, just to

talk about the adverse events.

DR. TURSI: Recognizing that the antibody titers were higher in that specific study consistent with kind of the scenario that was described, I can take you through the adverse event profile demonstrating no difference, if not actually an improvement in the adverse profile of AA4500 in those subjects.

I'll take you through the same adverse events greater than or equal to 5 percent, and the left columns represent those in the 857 trial, the first trial, and the lighter green on the right side represent those subjects in the 858 trial with higher antibody titers. And what you can see across the adverse event profile is whether we consider swelling of the hand, contusion or injection site pain, extremity pain, hemorrhage, tenderness, et cetera, all those adverse events, right down to injection site pruritus -- there are no differences, if not improvements, in the adverse event profile looking at that trial of 857 to the trial with the higher antibody titers in 858, suggesting that there does not

appear to be any risk consistent with duration of injection.

I could also speak to subjects who have long interjection intervals, specifically those in the five- to six-year range, and what that information demonstrates is that there was no difference in terms of the adverse event profile in subjects even if they received it as far as ten years between injections. So, again, supporting the safety profile of AA4500 in the presence or absence of antibodies.

DR. O'NEIL: Could I quickly follow up and ask how many of the people in 857 did not roll over into 858, or was it a complete rollover? By that I mean people who did not go on to the follow-up study may have indeed been those who were at higher risk for some reason.

DR. DELCONTE: Only six of those patients in that study did not roll over out of the 308.

DR. O'NEIL: Okay. Thank you.

The one other question that I had is after there were three people who had tendon ruptures, you indicated that you changed the injection technique,

particularly for PIP joint injection or injection near the PIP joint for PIP contracture. Do we have any evidence whether that changed the outcome? That is, did the complication rate decline?

DR. DELCONTE: We've actually looked at the number of injections before and after. Dr. Tursi will go through that.

DR. TURSI: What we noticed with the training reinforcement was essentially that there was an improvement in terms of the potential risk that ultimately patients would foresee with the injection. This was a training reinforcement timeline, and essentially, ahead of the training reinforcement, we had performed 734 injections, 446 MP and 288 PIP cords. And as you can see, the two tendon ruptures occurred.

At the time of the training reinforcement, that was followed by over 1800 injections, 1,027 MP cords and 869 PIP cords, and a single tendon rupture. And I think it's important to point out that our injection training and the entire risk management program is designed with this experience in mind,

taking the lessons learned from the clinical trials and ultimately improving them for inclusion in the clinical program training.

DR. O'NEIL: Dr. Haque? I'm sorry, yes.

DR. HAQUE: Thank you. I'd like to wrap up a few of my last questions. First, you had about 13 percent non-responders by the 50 percent improvement in contracture criteria, and 35 percent by the 5 degree criteria.

Any thoughts on those non-responders, or are there any clues as to who we should not bother to inject?

The second question would be, is there any data on the safety of efficacy of surgery after the injection? Did any of your patients go on to need surgery, and was there any increased tissue damage present or any other problems with wound healing?

And then I had a question on your -- in the brief that we got before this meeting, I read the instructions that you were giving out, and it suggested that for the small finger, you would inject more towards the palmar digital crease. And I was

concerned about that, because that's where the spiral cords and abductor digiti minimi cords tend to push the neurovascular structures.

DR. DELCONTE: Let me start with dealing with what happened and what we saw in some of the non-responders. What we saw sometimes of the patients who didn't get down to zero to five, that they did -- there were a number that had some improvement. Of the ones that did not get all the way down to zero to 5 after -- or didn't get three injections, some of them did not have any more palpable cord, and the AA4500 was able to disrupt the cord, but it didn't -- there were other factors which may involve the collateral ligament, volar plate that could impact the finger from being completely straight.

Dr. Kaplan can talk about there were patients who were operated on after AA4500.

DR. T. KAPLAN: Yes, I guess I got to have experience with everything. For a while, I had one non-responder who had a really thick -- and I think that he didn't -- I ultimately took him to surgery because he didn't respond, and he just had a really

big, thick cord. And actually, when we got to surgery, you could see an area where that cord looked a little bit thinned superficially, almost like there was a little divot there. But the cord didn't break. So he just had a really thick cord. He -- we tried good, hard manipulations all three times, and he just didn't rupture.

I did have another patient who I took to surgery. She actually had eight injections. She had three placebo injections, followed by five collagenase injections. She had three collagenase to the MP joint level, two injections to the PIP joint level. And you can kind of see I have a free elevator, a little surgical instrument here, pointing to an area of the cord just to orient the fingers pointing out towards the left here. And the cord kind of comes up, and you can see the section from about here to about here no longer looks as well-defined as it does here, or even out here, although I think this area out here may have been the site of one of the PIP joint injections.

But this is the site where I think I did most of the injections, and you can see it just kind

of looks a little bit chewed up a little bit, a little bit reddened. It doesn't have that same organized consistency.

But speaking to the technical abilities to do that surgical procedure, I didn't find that the tissue planes were obliterated. It was still relatively easy to identify the fat layer from the neurovascular bundles, to safely identify the core tissue and excise it.

And I think there was a third clinical part that I forgot.

DR. HAQUE: The palmar digital crease injection for the small finger.

DR. T. KAPLAN: Yes, actually, I did a spiral cord.

DR. O'NEIL: Could you repeat the question?

DR. T. KAPLAN: Oh, I'm sorry. The question was at the base of the digit, as we modified the technique, and if I can just switch gears for a quick second, I think with the modified technique -- again, I had the first patient who had a tendon rupture. So before you actually experience a complication, before

it’s ever happened, you aren’t as aware of it in day-to-day practice, at least I wasn’t.

Once I knew one patient had a tendon rupture, I think that you become a little bit more concerned, you become a little bit more attuned to the potential for the complication. And not only would potentially the location of the injection matter, but also I think one of the patients who had a tendon rupture was actually on their third injection.

There was a patient who had good restoration of extension, had not yet met that zero to 5 degree benchmark, but the investigator wanted to try to get it to that point, did a third injection. The patient had -- I don’t remember the -- had a contracture probably in the 15 to 20 degree range, the tendon rupture occurred. That in my experience, after the tendon rupture happened, once I didn’t have patients who didn’t have a full correction but I couldn’t feel a well-defined cord anymore, I didn’t give them any more injections. And I think that’s key to the training.

So it’s not just where you’re giving the

injection, but, hey, what we're treating is the cord. And if you can't feel the cord, you can't access it safely, don't give the shot.

But I think this is an example of the spiral cord. Again, the finger is pointing out towards the left, and there is a little blue marker here and a blue marker here, and I actually put surgical ink along that cord tissue. And what we can see is nerve and artery poking out here, the nerve and artery right here, and this cord coming from underneath to over top.

So it does. This cord tissue as the various areas of the fascial anatomy come together, they can wrap around these, but you can see a web space here. Here's a finger with the web space right in here. So right at that web, I think you can still get good access.

It is a small needle. Unlike needle aponeurotomy, you're not passing that needle back and forth. You're just injecting it right into that cord, and if a patient -- and you're doing that without a local anesthetic, so if the patient has a paresthesia,

you can stop, redirect.

DR. DELCONTE: And I do want to remind, we did not have any nerve or artery injuries in our series.

DR. O'NEIL: Are there other questions from the panel? Dr. Mazor.

DR. MAZOR: When you're talking about monitoring adverse events if this is approved, can you talk for just a moment about how you will assure that there aren't misses, that everything is reported and captured? Is there any system in place to maximize that? Are you worried at all that you will miss people?

DR. DELCONTE: Dr. Tursi can show you the targeted pharmacovigilance program that we've put in, or we propose to put into place that will minimize that. I don't think we can ever totally make sure we won't miss a case. But go ahead, Jim.

DR. TURSI: I can certainly reiterate regarding the enhanced safety monitoring program that we're suggesting for AA4500. This was from my main presentation. Things we'll include without

reiterating the entire slide, things will include the safety hotline. The aggregate safety review will be performed monthly for the first year. We will be specifically looking for potential problems, followed by quarterly reviews Years 2 to 5. And as I said, there also will be a follow-up questionnaire in the event of something like a tendon rupture, so we can track, gather more information and then potentially adjust our training program or distribution as we need to based upon those findings, with the ultimate goal, of course, being to ensure safe and effective use of AA450.

DR. O'NEIL: Next, Dr. Swartz.

DR. SWARTZ: My question is, we've already talked about treatment for surgery after injection, but how about the reverse? If a patient presents having had surgery and still has a contracture, are they still candidates for collagenase injection, and if so, what are the caveats?

DR. DELCONTE: Yes, we've had a number of patients who have had prior surgery that were entered into the clinical trial, and we've actually analyzed

the data. Here's the response rates. This is overall in the pooling of the three large or the double-blind trials, where about 63 percent in patients without prior surgery, they're in that same range. And then patients who've had surgery are about 60 percent.

And then if we can build this, we further looked -- because of the way we collected the data, we also looked at if they had prior surgery in the same finger. And there's really no overall difference in patients who had had prior surgery versus patients with no surgery.

DR. O'NEIL: Someone else had a question over here. No? Okay.

Any other questions? Oh, you, my neighbor, Dr. Buckley.

DR. BUCKLEY: Can you give me a little bit more detail on the safety monitoring post-marketing? So I'm looking at the slide and it'll be a safety hotline, which I assume would be for both physicians and patients to call in, and aggregate safety review monthly and then quarterly. Are these going to be questionnaires directly to the physicians who did the

procedures?

Are patients going to be surveyed? I'd imagine if patients had a procedure, they might not be coming back for regular follow-up a year, two years or five years later. So how do you get that data other than patients remembering to call in or remembering that there is a hotline? Will there be some kind of regular survey both in terms of results and in terms of adverse events?

DR. DELCONTE: There wasn't a regular survey for patients.

Jim, do you want to address that?

What we plan to do in the targeted pharmacovigilance is part of the patient information brochure. We'll actually indicate what some of the side effects are to look for, and then we will have a hotline which will be available for physicians as well as patients. And we'll be able to transfer these directly to our safety group for evaluation, whether it's patients or physicians.

If patients aren't following the instructions and don't return, we don't have a

mechanism for that. It's the ones that do return that we have the mechanism for.

DR. BUCKLEY: So -- but am I wrong in thinking that many patients might not return? It's not like a rheumatoid arthritis patient who's coming in every three months for monitoring. If they're seeing someone for a surgical procedure, unless -- I'm curious about if you have estimates about how many of those patients are going to be coming back. Is there some protocol that you'll be following a certain group of these patients every three months or once a year, and how of those patients would it be?

DR. T. KAPLAN: I think that -- and I have another just kind of example, but with collagenase, all the tendon ruptures happened relatively soon after the treatment was given, within one to two weeks.

Another example that I run into is now with distal radius fractures, plating of distal radius fractures, where we put a metallic plate on the surface of the radius in order to stabilize that fracture, has a risk of tendon rupture. And we've put them now on the palm side because we think that's more

safe, but patients can still later develop a problem. And I usually the last day I see a patient after their fracture, say please call me if you start having any pain on this side of your wrist, and I've had several patients come back two years, three years after treatment who've had irritation.

And when I took them to surgery to get their plate out, could actually see areas of the tendon where it had been ruptured -- where it had been thinned.

It's well-recognized now that patients won't come back sometimes until a rupture actually happens. So I think it's difficult to kind of capture every patient and to baby-sit them completely, but what we can do is make sure that patients are aware of what to look out for, make sure that physicians are aware of what they need to look out for, and provide mechanisms for them to contact us if something happens.

DR. BUCKLEY: I guess I'm still a little concerned that there isn't a regular way to follow-up these patients, not just in terms of adverse events but to know how long they maintain the benefits. It

doesn’t sound like we have any way other way other than patients remembering to call us, or somehow remembering that a year ago they had some material that they may not have anymore.

DR. DELCONTE: And that’s the -- I guess, limitation of any type of therapy, that sometimes satisfied patients don’t come back. Patients with problems come back, and that’s why we’ve started the two- to five-year follow-up study, so that’s taking that large cohort we have in the clinical trials and following them up through five years to get that long-term result. So that will add to the knowledge database of what happens long-term both in terms of recurrence, progression of disease and safety.

DR. O’NEIL: All right. If there is no further discussion, then we will proceed to the next session, which is to discuss amid the panel members the questions to the AAC.

The FDA has provided us with three questions. The first is as follows: Investigator training in the clinical studies included injection technique instruction via manuals and DVDs, workshops

and investigator meetings. This may be more extensive than the training proposed for the education of healthcare professionals in clinical practice if the product is improved.

They ask us to please discuss the adequacy of the proposed training.

And I think an easy -- well, you want to -- I thought an easy way to do this might be to go around, so we'll start with you, Dr. Weisman.

DR. WEISMAN: I think the answer to this question has to be put in the overall context of what the mitigation strategies are that we're going to suggest, and that's how I could answer it. Kathleen has advised us that the mitigation strategy should be commensurate with the risk. It shouldn't severely restrict access, and it shouldn't be burdensome on the healthcare system.

So thinking about this issue and the discussion around the room and the table, obviously, a suggestion like restrict this procedure to only board-certified hand surgeons or certified hand surgeon, that would be unduly restrictive of access.

On the other hand, leaving the whole process to a voluntarily system that was based upon something that worked with a highly selective group of skilled individuals, and then extrapolate that to an unselected group of individuals, where we don't know whether it's going to work or not, might be too loose. So that would be the extremes.

And so as I'm thinking about the discussion here, I'm thinking that what really fits the ideal to me way to do risk management here would be a mandatory registry. This would answer Lenore's concerns, which she's brought up several times, that how are we going to know whether or not the folks that actually get this procedure are really monitored long-term, because there's going to be fallout on either end, the ones that do well and the ones that do poorly.

A mandatory registry also has the advantage of getting data, which we don't have. It also has the benefit of casting a kind of accountability to individuals who both the company, the FDA and to physicians who participate in this, that they know they're going into a mandatory registry. And so you

don’t really get into this lightheartedly. So I would think that with that level of accountability, then it might work.

I’m sorry if I put the cart before the horse here in answering this question, because I don’t think that the investigator training in the highly selected group of individuals that participated in this study is necessarily the appropriate way to go to unselected individuals out there in the world. And I don’t think we can fix that, because we don’t know anything about how it works. So getting off that stage, I would move it more toward the idea of a mandatory registry, which would have those advantages that I just mentioned.

DR. O’NEIL: Yes, sir, Dr. Rosebraugh.

DR. ROSEBRAUGH: Yes. This is Curt Rosebraugh. I just want to probe that answer a little bit more.

So I have to tell you, are you saying a mandatory registry for every patient that would be treated with this?

DR. WEISMAN: At the outset, yes. A prospective collection of data on the first year or

two or the first numbers that our statisticians would tell us would be appropriate to know exactly in which direction we're going.

DR. ROSEBRAUGH: Okay.

DR. WEISMAN: We can figure that out. It wouldn't be forever, but it would be for the specific goals of seeing whether or not the risks of this have exceeded what our expectations are.

DR. ROSEBRAUGH: The reason why I'm asking is, registries come in two flavors. So we have a lot of drugs like the TNF drugs where we have registries that are not part of a REMS. They're a part of a post-marketing requirement where we say, well, you know, why don't you register a certain number of folks and let's follow them for a while and get more data. Then we have registries that are part of these Elements to Assure Safe Use. And I just want to make sure you understand that when we talk about two ends of the spectrum, we consider that pretty far on one end of the spectrum.

In fact, we very seldom have programs where we register every patient that gets treatment. It's

very extreme for us to do that.

DR. WEISMAN: Well, it works in Europe, where the mandatory registries have given us good data on the risks of anti-TNF drugs. The registries in the United States have not given us good data, and we don't rely on it.

DR. ROSEBRAUGH: I appreciate your views. I just want to make sure everybody understands that is not something we've routinely done, and it would be one of the more stricter REMS that we've put in place.

DR. O'NEIL: Mr. Brackney?

MR. BRACKNEY: Well, from a patient's standpoint, we've talked about it earlier. You don't want to do anything that's going to limit access. Even as an orphan drug with a small population, you still have to make sure there's doctors out there that can administer the drug, because clearly, there is an advantage to people with the disease to have this treatment as opposed to surgery. So I would be concerned that the training is sufficient and the base of the doctors available is as widespread as possible.

But I would at the other end get worried

when there's somebody says other. When I see an other category on their registry for certification with the docs, then I worry about how is the other and are they, back to the point, trainable? I mean, no offense, but not every doc is trainable.

So I would say sure, beef this up as much as you can, and then be very selective at the outset going out with who you have doing it and the doctor and the practice, and as much as we can, register the patient so we know what the outcomes are of the people that are administering the drug, so that we know there is benefit and that we don't have a hidden problem somewhere for an untrained person giving -- not taking the training correctly and administering the drug.

DR. O'NEIL: Dr. Weisman had a reply.

DR. WEISMAN: Can I answer the question? Now, it's only after years of concern that now we're getting to the point where Congress is mandating registries of drug replacements. And they're very concerned about outcomes of hip and knee replacements, and that's being fed back into large grants being announced by the AHRQ and other organizations after so

many years of the voluntary registries not giving us the information in the United States that we need.

And so I wanted just to respond that voluntary registries have not been very useful to -- and I understand your concern about perhaps the onerous issues of having to maintain it, but that could be a subject of negotiation between yourselves and the sponsor as to how that actually gets carried out. But taking it up that level I think is something that should be considered by the panel here.

DR. O'NEIL: Ms. Aronson.

MS. ARONSON: I guess I'm trying to weigh in on the words "may be" in the second sentence. So it's a little confusing about the -- it doesn't say is more, will not be as extensive, and I believe that's the presentation that we had. So I just wanted to be clear on that "may be." That, for instance, I don't think there were investigator meetings, and I'm not sure what other things might be dropped from the list of training.

DR. SAAG: I want to largely second what Dr. Weisman has said, and I do recognize the FDA's

viewpoint on the costs and consequences of comprehensive registries. But I think as Michael has illustrated, it's time from a public health perspective to contemplate new models, whether the sentinel nodes or some other similar mechanism that is soon to get started might provide sufficient surveillance to look at some sample, not a voluntary registry but some sample of patients who are started on this therapy, particularly those who might be treated by physicians with less historic expertise in doing such procedures, could be done as something the FDA will have to consider.

But that would be what I would consider it optimal. And I guess it relates to getting back to the question, and I would answer the question as "no" in terms of rheumatologists. The average rheumatologist does not have enough knowledge of the anatomy of the hand and experience performing manipulations after injections, or managing, differentiating postinjection inflammation versus infection to without significant training be able to safely administer this product.

I think that there is reason to think that with substantial training that there would rheumatologists that I would feel confident doing this, but short of a more extensive training program, I would have serious reservations about the average rheumatologist administering this product.

DR. O'NEIL: Dr. Buckley.

DR. BUCKLEY: I think I'm essentially in agreement. I think that this study has showed us that there is a real role for this drug, and I think it's going to be a very beneficial treatment. But I think the data that we have is on its use and the results of its use with hand surgeons and orthopedic surgeons, and we just don't have the data here to tell us whether other kinds of physicians, including rheumatologists, will get these same results.

I hope that's true, but I think that if we sort of jump ahead to the next question, unless there's data to say that's true, I wouldn't feel comfortable saying it's a leap of faith, but we think they can do it based on the number of rheumatologists in this study.

DR. O'NEIL: Dr. Olsen.

DR. OLSEN: Well, I have a slightly different take. I think that the benefits look significant and the risks look low, and I think that the plans that have been proposed -- I wasn't -- I didn't have that opinion before I came to this meeting, but after having looked at these pictures and video of demonstrations, I think many of us could be trained to do this if we felt comfortable doing this. And we do things every day in our offices that are totally unregulated. You could put as much glucocorticoid in as many tendons of somebody's hand as you wanted to at the moment, and that's probably a higher risk.

So I think by going through what's being proposed here, registering, have limited access, I think it sounds like something that would work and would make something available to a relatively small number of people who sound like they need it.

DR. O'NEIL: And by registering, you mean registering the healthcare provider who delivers?

DR. OLSEN: Oh, I don't want to get into the

registry question. I did like the idea of a registry, but I do understand that's probably a big -- maybe it could be a sample registry or something like that but not biased in some way, like figure out some way. The statisticians could tell us some way to get an unbiased sample and follow that sample, because I agree, we need more data. But within the confines of this being a rare disease and it looking like it has benefit, I think that shouldn't hold it up.

DR. RAPPAPORT: Just to be very clear, the sample registry is a study, and the other is just collecting everything and mandating that a patient has to be registered before they can get it. It's a whole different ball of wax, but the study is something that we could, as Dr. Rosebraugh said, do under a post-marketing requirement.

DR. O'NEIL: Dr. McAlindon.

DR. McALINDON: So I think when you put this intervention into the context of the alternative surgery, the data show that it's relatively safe. Also, as an orphan drug, I think the primary point of this is to make it available to people. So I'm

concerned about restricting access. There are, of course, issues of generalizability, but I don't think necessarily that this panel of hand surgeons is necessarily generalizable to hand surgeons in the population.

So I think that the training proposed is likely adequate for clinicians who are accustomed on a regular basis to doing interventions in the hands. And I think that some sort of surveillance is necessary. I think that the registry would be the gold standard for such surveillance, but an alternative would be to have the registration happen at the level of the clinicians so the clinicians would be registered. And the advantage of that would be that it would recruit essentially clinicians that had a more intellectual interest or academic interest in performing this procedure rather than one in simply increasing their practice volume.

They could then keep a record of patients on whom they performed this intervention, and that could be used to address questions which I view as being perhaps more of a Phase 4 nature, looking at the

quality of care and the long-term safety. That to me would be optimal scenario.

DR. O'NEIL: Dr. Mazor.

DR. MAZOR: I can't talk to the medical and surgical issues, but I think that one of my concerns would be that if there is training, and it sounds like very -- a lot of thought has gone into the training. My concern would be that people go through the training and that this issue of kind of doing ones e-mail simultaneously be somehow addressed, that there be some sort of check that whatever physician or surgeon went through it had actually gone through it and not just signed off on it.

And I think what I was trying to ask about the adverse events before was related to what you're all calling surveillance and registries, that there needs -- that these questions really, some of them aren't answerable at this point. In some way, we need more data to say, well, is there a difference between rheumatologists and others in terms of these adverse outcomes. And I don't know what the options are and what form that might take, but it seems critical.

DR. O'NEIL: Dr. Kaplan.

DR. S. KAPLAN: A few thoughts. In terms of follow-up and monitoring, it's difficult for me to get patients with problems to come back to the office to be seen. I don't know how we're going to mandate that people who are doing well are going to come back. The Stanford study I referenced was one of the Phase 2 studies. They had 23 people. Nine came back. They were only able to get nine to come back, one of whom received placebo. So I don't see how we can easily monitor this other than keeping in touch with the providers who do the actual work, to see what kind of complications they're seeing.

As a surgeon, I'm very familiar and comfortable with credentialing as it relates to operating-room-based procedures. Delineations of privileges is something we encounter frequently. The concept of what we're essentially trying to do here is credential people to do things in their office. That's a different world I'm neither familiar nor comfortable with. There's a lot of things that are going on in the office -- I agree with Dr. Olsen --

that people are doing that we have no idea about and nobody's watching. People are injecting varicose veins. There are laser treatments for a variety of things.

I think the onus is on the physician. The physician states that they're comfortable in this area, does the appropriate training. I think they are a licensed physician, they should be credited for deciding themselves what they're comfortable doing. I have biases. I think I will do it better than somebody else. The number three study, Larry Hurst, he got better results than anybody else. That doesn't mean other people shouldn't do it.

The level of complication, I agree with Dr. McAlindon. As a surgeon, a tendon rupture is awful. It's worse than the open procedure for Dupuytren's, yet at three per 1100, I'm comfortable with it. It's certainly less common than the rate of nerve injury either with the needle aponeurotomy or open surgery. It's less common than the risk of infection. So I'm comfortable.

So this specific question, as I understood

the proposal, I think that the training is more than adequate.

DR. O'NEIL: Dr. Swartz.

DR. SWARTZ: Thank you. It takes a long time to see 73 patients with Dupuytren's in most hand surgeons' practices. Most hand surgeons do five operations, for the large part: ganglion cyst, carpal tunnel, trigger finger, de Quervain's releases and maybe one other procedure. This is a pretty unusual patient even in a practicing hand surgeon's office.

In a rheumatologist's office, in my opinion, there aren't any patients with rheumatoid arthritis who have this disease. I've never seen one in 30 years. It's unusual for a rheumatologist to see these patients. Now, making the diagnosis of a Dupuytren's nodule instead of a rheumatoid nodule is an important distinction, but these aren't the patients that will be treated.

So having said that, I think first of all, the training of video DVD is adequate, that, in my opinion, the doctors who should take care of these problems are doctors who see these problems on a

regular basis. What the level of their board certification is is less important than their familiarity with the disease and its surgical complications.

And lastly, it's my opinion that people who treat any disease entity should do so if they can manage the complications of that disease entity. The complications here are pretty rare, but they're devastating. A ruptured flexor tendon may not be a recoverable situation, and a physician bears that responsibility.

So with those caveats, with those warnings upfront from the company to the doctors they're marketing to and the information to the patients that they're going to be providing the medication for, I think I'm okay with this training and the program that's been outlined by the company.

DR. O'NEIL: Dr. Haque.

DR. HAQUE: Thank you. I am also pretty comfortable with the training regimen that they have, but I do agree with Dr. Mazor that somehow we have to enforce that the training's actually done. And I

would recommend that the self-assessment exam that the company has already proposed just be made online, and that the treating physician actually have to pass it to get certified. It's the only way that you have of really enforcing any way that they actually watched the DVD.

As far as healthcare professionals and their level of training to do this, this actually seems like a relatively simple procedure. The cords that we're talking about are usually fairly superficial, as Dr. Kaplan said, and I think that I don't know how many rheumatologists actually see patients with Dupuytren's. I was surprised to hear several rheumatologists here questioning the ability of the average rheumatologist to do this procedure, but I think that this is not going to be such a huge volume issue that people are going to get rich off of this procedure.

In that situation, I'm more worried about Dr. Swartz's concern about off-label uses.

I think that people who are seeing enough of this that they actually are willing to take the effort

to sign up and get the DVD and take the test are probably going to be well-qualified to do this.

DR. O'NEIL: Dr. Kaplan has another comment.

DR. T. KAPLAN: Xiaflex, I guess, comes under the purview of this rheumatology committee because, I guess, nobody really knew where to put it. So the conversation comes up between should it be a rheumatologist or a hand surgeon.

But many of the people I know are in a very large orthopedic group. They have a hand surgeon or two. They have a physiatrist or two or three and maybe a rheumatologist or two, and even musculoskeletally oriented family practitioners or internists. I think that's more likely the scenario. I don't think it's the patient with rheumatoid arthritis who says to their rheumatologist, oh, by the way, what is this in my palm? So I think as we think about it, we think about it as hand surgeons, as orthopedic surgeons versus people who are caring for musculoskeletal problems. I think that's a much more likely scenario, and I'm still comfortable with it.

DR. O'NEIL: One comment that I had since I

passed my chance on the way through. When you asked how many rheumatologists actually see these patients, I'll tell you that as a pediatric rheumatologist, I haven't seen one since I was a medical student.

But the PM&R, the physiatry physicians are very likely to see some of these patients, I think, and we should include them in the training program, because they may be as likely as a rheumatologist, certainly maybe even more likely.

And from my perspective, I think the proposed training looks very good. After sitting through this and reading through the information we were presented with prior to the meeting, I feel like if I were ever to see one, I might be competent to do it, having put needles in all kinds of obscene places.

So I think that it does look like a fairly simple procedure. In my mind, I agree completely with Dr. McAlindon. It looks like it's a very low rate of although severe complications, it is quite low in good hands. And hopefully, the training as proposed and the registry of the trained practitioner will allow the company to maintain contact with the practitioners

who are doing this, and perhaps every few months by e-mail or by direct mail, inquire of them if they have seen complications that they need to report, and thereby sort of enhance reporting of adverse events.

We've got a couple more comments from the docs, and then Dr. Okada had a comment.

Dr. Weisman.

DR. WEISMAN: To follow up on your comments, Kathleen, what we've heard is that there's a low rate of complications, but when it occurs, it's quite severe, flexor tendon rupture. And if a rheumatologist does one of those for whatever procedure they do, if it's injecting an Achilles tendon sheath, a biceps tendon, it happens once. They'll really remember that. And the -- so I have concerns about it.

And the other is from our colleagues on the panel here, they've told us in so many words about the inadequacy of the follow-up of these patients. Dr. Kaplan says he doesn't expect to see the ones that do badly or see the ones that do well, which would be the majority of people who get the procedure. So the

voluntary system of following these patients is really quite inadequate. There has to be some improvement on that, just -- that's my response to what I'm hearing around the table.

DR. O'NEIL: Well, I was trying to propose sort of a middle ground which was enhanced follow-up, enhanced reporting, which may be working in some other diseases, but I take your points well, that, yes, we don't have complete reporting in this country for virtually anything.

Dr. Saag and then Dr. Okada.

DR. SAAG: I just want to first of all clarify my comment from earlier, and I'm not suggesting that I don't think rheumatologists should be allowed to do this procedure. But I feel very strongly that the level of training provided, while perhaps sufficient for orthopedic surgeons and particularly for hand surgeons is adequate, I do not believe at all that this level would be adequate for most rheumatologists. I would venture to say that most rheumatologists have no idea where the A-1 pulley is.

And in contrast to comments made about getting more comfortable as the presentation went on, I became less comfortable listening to some of the nuances of how to properly position the injection, and believe that just watching a DVD and taking a test, for example, would be fully inadequate in assuring the appropriate and safe administration of this by physicians who are not skilled in understanding the hand anatomy.

I think that there are certainly things that could be done that would not be terribly extensive that could substantially enhance training, such as tutorials. There was mention of working with cadavers, the possibility of developing a model that would demonstrate the appropriate positioning of the injections, things that would dramatically improve the confidence in a physician who normally does not focus on hand anatomy in administering an injection into the right location.

I would go further to say that most rheumatologists in practice don’t have office staff that even know how to put on the bulky dressing. Some

do work with orthopedic groups. That's true, but many do not. And there's going to be some training needs just in understanding the post-procedure care. Again, I don't believe that a DVD and a examination afterwards would be sufficient in bringing these physicians and their office staff up to speed, but I do think there are things that could be done to ameliorate that concern.

DR. O'NEIL: I'm going to let Dr. Okada go next, and then we can get to you, Dr. Buckley.

DR. OKADA: What I was going to say was actually touched on by Dr. Rappaport and Dr. Rosebraugh already. Our concerns related to not knowing how to generalize the study results are not ones that necessarily have to be sort of all or nothing in terms of mandatory registry or nothing. We do have the post-marketing requirements, and we could potentially, for example, ask for a large simple trial, where essentially, you just take all comers of physicians that would be allowed to utilize the product, and follow them for a certain period.

Something like that might be more feasible

and less restrictive on the general public than, say, a mandatory registry of all patients, so I just wanted to raise that possibility.

DR. O'NEIL: Dr. Buckley.

DR. BUCKLEY: I guess I have two other comments. One is about access and just one is about the generalizability of this procedure to other types or a broad variety of providers. I think the -- if the plan was for this product to have it be a product that would be used by a broad array of providers, then I think this study should have been designed to look at a broad array of providers. As it is, it looked at very talented array of providers. And I just feel, if I was designing a treatment that required a certain level of skill, if I only picked the most skilled people, then I think I'm going to bias those results to the best results. That's fine if that's who's going to be using it.

But if really the intent here was this product was going to be able to be given by many providers, I think that's the way the trial should have been designed.

And the other thing is, to go back to this access issue, so if there's a condition that's prevalent in the population and the provider that you need to go to, you need to see on a regular basis. Maybe you just need to see that provider every two or three months over many, many years. That's a big access issue if your provider is an hour away, two hours away or three hours away. If this is a procedure that will give you a year or many years or a lifetime benefit for a significant disability, I would bet in that situation, you'd be more willing to get in the car and drive an hour and get that procedure done by somebody who's done it many times.

So the access issue, I don't think is quite the same access issue as, for example, someone with rheumatoid arthritis or juvenile arthritis who is really talking about many years of trying to get to a provider that might be too distant, and I think we need to weigh that when we think about it.

DR. O'NEIL: Dr. Olsen.

DR. OLSEN: Well, I just want to point out that the idea that an initial trial is not broad and

that it doesn't include all kinds of scenarios is exactly what happens in the approval of all medical interventions that we do. All of the initial TNF trials excluded people we thought wouldn't get the drug, and then when the drugs are released, we start giving to those people and learn new things.

I recently did a small trial in osteoarthritis of a new potential treatment, and I wanted everyone to do a 25-foot walking time. If you came in with a walker, I excluded you. Now in real practice, I'll probably want to see what happens with those people. But in my first trial, I don't want to do that. So this is just what you're facing in trials.

So I think that's where a Phase 4 or a post-marketing trial would be very useful, just collect more data. It's the same thing that happens in drugs is what I want to point out.

DR. O'NEIL: Dr. Kaplan.

DR. SAUL KAPLAN: I do think it is an access issue. If it requires up to three injections per joint per affected finger and you can only do one at a

time, people don't come in with one affected joint. They come in with multiple joints, multiple fingers, both hands. So I think -- and you have to come back the next day after the injection, so I wouldn't belittle the access point. I think these are -- multiple visits are going to be involved. More visits with this procedure potentially than with surgery.

DR. O'NEIL: I'd like to ask the representatives of the -- oh, another comment.

DR. McALINDON: Very quickly, access issues are not necessarily geographic. Insurers can effectively limit access to quite small domains. If the one hand surgeon in that domain chooses to not do this procedure in favor of doing surgery, that could pose limitation. And so including clinicians who are perhaps nonsurgical but have some skill in hand procedures could improve the access.

DR. O'NEIL: Now, I'd like to ask the FDA representatives if there are any other points they would like for us to address.

DR. OKADA: No. Thank you for all that discussion. That was very helpful.

DR. O'NEIL: All right. Thank you. We will move on to Question No. 2, which if I can find it among the many papers I have here, I'll be able to read to you. This is a voting question, and so I will first read the question and then give you instructions regarding voting.

In view of the data available for safety and efficacy, do you recommend approval of Auxilium's clostridial collagenase for the treatment of patients with advanced Dupuytren's disease?

And the voting procedures are as follows: We will be using the electronic voting system for this meeting. Each of you have three voting buttons on your microphone: a yes, a no and an abstain. And these are flashing before you now. Once we begin the vote, please press the button that corresponds to your vote. The vote will then be displayed on the screen. I will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and the vote into the record, as well as the reason they voted the way they did.

I will once again read the question, which you can see on the screen in front of you.

In view of the data available for safety and efficacy, do you recommend approval of Auxilium's clostridial collagenase for the treatment of patients with advanced Dupuytren's disease?

Please vote.

We may have an AV issue.

Dr. Haque's -- okay. Good.

We're missing one person. So we don't have a full vote.

We will need to repeat the vote. I ask those who cast their vote to use the identical vote that they did before. Please don't change your mind and flip flop, and what we should see now is a compilation of 12 votes. So if everyone could please vote now. So when the lights do come on, we will do the second vote. Please vote.

For the record, the voting results are yes, 12; no, zero and abstain, zero to recommend approval.

Dr. Haque, would you like to begin stating your name, your vote and the reason for your vote,

please.

DR. HAQUE: My name is Mustafa Haque, and I voted yes to approve this medication because I do think that it will provide significant benefit to patients, and the overall safety profile looks good.

DR. SWARTZ: William Swartz, I voted to approve this drug. I believe that the risk/benefit ratio is very low. The benefit is very high, and I very much appreciated hearing the testimonials of the patients that have received this drug. That did not necessarily sway my vote, but the vote was made on the merits of the scientific work presented to us.

DR. S. KAPLAN: Saul Kaplan, I voted to approve the use of the drug. I view it as another option. I remain -- or I want to be convinced that the long-term results are going to hold up enough to make this something that will become the mainstay of treatment. I'm worried that this, like surgery, will not be the ultimate answer.

DR. MAZOR: Kathy Mazor, and I voted yes based on basically the discussion among the physicians and surgeons, which I again have no medical expertise.

The patient testimonials were important about thinking from the point of a view of a patient. And the limited understanding I have of the medical understanding here, it seems like the appropriate decision and also the FDA's comment that this is also not a forever decision, that there are additional studies that could potentially happen in the future and that things can change if needed.

DR. McALINDON: Timothy McAlindon, I voted yes. There's an acute need for a nonsurgical intervention for Dupuytren's. This product appears highly effective, and it has a safety profile that is acceptable and better than the current surgical alternative.

DR. OLSEN: Nancy Olsen, and I voted yes. And I agree completely with the comments that were just made, and I also thought that this satisfied an unmet need. So it will be very helpful to the individuals with this disease.

DR. BUCKLEY: I'm Lenore Buckley, and I also voted yes. I think that this is a treatment that offers patients who have significant disability

significant benefits at an acceptable risk.

DR. O'NEIL: Kathleen O'Neil, I also voted yes because this is an effective and reasonably safe alternative to surgery, and in fact, in some ways may be better than surgery.

DR. SAAG: Ken Saag, I voted yes based on a highly satisfactory risk/benefit ratio and unmet need.

MS. ARONSON: Diane Aronson, I voted yes for the reasons that have been said.

MR. BRACKNEY: Bill Brackney, I voted yes because it is a better alternative than surgery, and in the long-term and holds a lot more promise for a permanent solution than surgery does today.

DR. WEISMAN: Michael Weisman, I voted yes because of the evidence in two very well-done trials and the significant unmet need.

DR. O'NEIL: Thank you, Panel. Now that we have voted to recommend that this be approved, we are asked the following questions -- we are asked the Question 3-A: What additional studies, if any, should be conducted post-approval to further assess the safety of the product?

Dr. Weisman, we know you've made up your mind.

DR. WEISMAN: No.

DR. O'NEIL: No?

DR. WEISMAN: I strongly suggested a mandatory registry, the details of which can be worked out as to how what kind of sample and who exactly is going to do it and pay for it, and how long it needs to be carried out. I think the statisticians would be very helpful in that regard. I understand that it's breaking new ground, as Bob and Curt have told us since they've really not done this before, and it does represent at least in their view a somewhat onerous responsibility.

But on the other hand, what I've tried to point out is that the voluntary registries that we've had so far in this country have really been inadequate to answer the important questions posed by biologic drugs, even non-steroidal anti-inflammatory drugs and most all drugs. And, also, the comments from our colleagues across the table here who've told us about the routine, usual follow-up of surgical patients or

procedure patients is very inadequate. And so that's the reason I propose this.

DR. O'NEIL: Before we proceed with this portion of the discussion, I asked Nicole to put up Slide No. 7 first of the FDA's presentation, just to remind us of the difference between the proposed post-marketing surveillance that was offered by the company versus an enforced and mandatory post-marketing, and these were brought by Dr. O'Connell.

We could -- we are suggested to use some or -- I'm sorry -- such recommendations may be important in a setting where one or more of the three dashed points here are in effect, and I think that the second dashed point, the product has serious risks that could affect the patient's decision to use or to continue to use the product, is applicable to this particular compound.

And then the next slide, just to remind you that the FDA-approved materials used to aid sponsor implementation of REMS and/or inform healthcare providers about serious risks. I'm sorry. The one

that I really wanted was the following one.

That we have to remember that mandatory here is that the FDA requires and enforces this, and then in Slide 10, that the REMS ETASU program would provide the most strict control over whether the product is used per FDA-approved labeling. But the downside is that it can impose burdens on the healthcare system and reduce access to care. And so they recommend that the ETASU program be used only if the product would otherwise not be approved due to specific serious risk listed in the labeling.

So as we discuss this, we want to make sure we keep straight what studies need to be done and what post-marketing should be mandated or used.

DR. ROSEBRAUGH: Can you go back a slide? So let me just kind of go over this a little bit, because this can be very confusing to people, and I have to admit it’s confusing to me. And so I will also say that this legislation is sort of a work in progress, and so we sometimes don’t know how to apply it until we get a case to work on with it.

But mandatory enrollment of patients for

this particular segment in reality means that in order for the drug to be used safely, you need to register the patient and make sure they're followed. So if you were giving a chronic medicine where you thought it was vital that you thought they had to have a CBC such that you would not approve the drug otherwise, then you would require that patient be enrolled so that we, we the government, could make sure that they were getting a monthly CBC. That's really what that means.

That's a little bit different than saying we need more data and I want to know the outcomes of patients. That is really more a post-marketing study, where we can say we can require the sponsor to enroll so many patients in a post-marketing study and say we want that followed, we want statistical analysis and all that kind of thing.

So these are two different things, and I just want to make sure people understand it, because as with any bureaucracy, it can be kind of confusing.

DR. O'NEIL: If I might give an example of mandated follow-up and mandated registry, the thalidomide story probably fits here as a mandated

situation, where physicians are trained in the issues related to thalidomide. The company will not allow you to write a prescription without performing that training. Pharmacists are also registered to dispense the drug, but only with appropriately trained physicians -- and particularly in females, pregnancy tests must be done monthly. And if there is no evidence of that, the drug cannot be dispensed.

So that's a mandated program that's in the works currently and has been for years.

DR. WEISMAN: To try and respond to Curt's question and I think I understand it, what is our concern here, the concern really has to do with the variability of the skills and ability of the physicians out there to be able to perform this in a way in which perhaps this voluntary educational program may not be adequate. We're not sure that things match. That's, I think, the biggest concern.

So what would be the best approach to that kind of an issue? And I'm not sure that a post-marketing study really helps us answer that question. That's where I'm trying to see -- I'm

trying to connect the dots here -- or should a registration situation that you described, where there is an ability to go back and document and take a look at what happens to patients going forward might be a more adequate way of approaching this question.

It's not like a situation where we're looking at risk of a drug or a procedure that's at the 1 percent or below level, where you can survey out there in a post-marketing situation and where there is little concern about who's actually giving the drug, there's more concern about the patient and the response.

Here, there's concern more on the front end, and that's why I'm bringing this to your attention in this way. What's the best approach, say -- to ask our FDA colleagues what would be the best approach that they think would be most suitable to answer the question about who is using this drug and what safe manner, and is the educational approach adequate to protect us from this? I'm trying to focus this on what the issue really is.

DR. O'NEIL: Dr. Swartz.

DR. SWARTZ: I'm not sure that is the issue. Intellectually, it might be interesting, but the real issue is what's the real rate of tendon rupture, because that's the complication. It takes 73 patients to be treated before one tendon rupture was found in this study presented by the sponsors. And so it's going to take a large number of treating physicians to come up with meaningful numbers over a significant period of time.

And there's another option that I think is useful than to have a mandated registry, which I think would be onerous and I'm opposed to. That is, there are two associations and societies of hand surgeons in the country that will be taking this on very quickly. There are academic centers that see large numbers of patients that will be eager to study these patients and their treatment thereof. There probably will be funding dollars provided not only by industry but also by grants from the societies that are interested in hand problems, and I think we can get -- while it won't be the most comprehensive study overall, it'll be meaningful in what the real rate of tendon rupture

is.

I think that's a pretty good compromise, compared with the onerous problem of mandating that the doctors drag their patients back into the office over an extended period of time when it's not likely that that can be done. And there are some precedents for this sort of thing, and so I would be in favor of a post-market study that could be done in a hybrid manner.

DR. O'NEIL: But, again, one problem is that if we do it through the plastics and orthopedic hand surgery route, we are not going to be capturing the family practitioner in Elk City, Oklahoma who may have 10 patients in their practice.

DR. S. KAPLAN: I bet you will, because the family practitioner is not going to be repairing the tendon rupture. So only the farmer who don't want to take the time to get his tendon rupture repaired will be lost in that circumstance.

DR. O'NEIL: I sit corrected.

Dr. Olsen had a comment.

DR. RAPPAPORT: Can I make a comment? I

think that the concept here is we can do a study, and we've said this a couple times now. But I just want to make it clear. We can require a post-marketing study, and we can talk about what the best way to do that is, who should be practicing, whether we should include different specialties and all that versus this mandatory registry.

And in general, we pretty much think that randomized controlled trials give us better information, cleaner information about just about anything. So trying to tease out the type of information that we'd like to get here about the safety and who should use this from a registry is going to be my mind far more difficult than from a controlled trial.

DR. O'NEIL: Dr. Olsen, did you have a comment?

DR. OLSEN: No, I was going to say exactly that.

DR. O'NEIL: Okay. Dr. Buckley.

DR. BUCKLEY: I think that if the FDA decides to approve this drug for use as recommended,

then I think a post-marketing study is going to be necessary. And I think it's going to be necessary to look at two things. One is safety, and safety across different kinds of providers, but even within providers, safety depending on how many injections that provider does. And also long-term results, this question, are we going to see rare systemic allergic reactions that we're really not going to know about until we get more patients, and how long are these beneficial results going to last? And in a real world or in a broader setting, is the efficacy going to be as good as it looks now?

But I think I take a point with the registry issue, because I think one of the things that this prospective trial might not tell us is high-risk groups. What about the person, the high-risk rate of this in people who have liver disease or alcoholism patients who might have more of a tendency to clot or bleed, diabetic patients? I think what these real world registries can tell us is outside of the defines of this clinical trial, in the real world, are there more infections, are there more complications, are

there more ruptures if you have diabetics in this group?

So I think probably the way to go initially is a post-marketing study.

DR. RAPPAPORT: I actually don't agree, because you still get into how do you tease out the background noise from the registry. But as I said, we can design a trial just about any way we want, and broaden the enrollment to include people at various risks. And it'd be a larger trial, but it's going to give you that information because you got a control in it. And those are important issues.

DR. SAAG: So I want to put on a pharmacopoeia head and not take direct issue with what you're suggesting, Bob, but at least suggest that some of our current technologies for studying drugs, devices and biologics maybe are a little bit old-fashioned. Clinical trials are great for establishing efficacy, but we know they're terrible for looking at safety. And when we see a safety signal in a clinical trial, it should make us particularly concerned about what's going to happen in the real world.

Registries have the limitations of observational data. What would be ideal here is to do a large simple comparative effectiveness study. The problem is there's nothing really to compare. We don't think that surgery is a good comparator, and I would be surprised in a Phase 4 study whether you could really randomize a representative group of patients. If I saw the results from this and had a drug that was approved, I wouldn't want to be in a clinical trial. I'd want to get the real thing.

So I think we're in some ways stuck with some sort of an observational approach, and again, back to the idea of sentinel nodes, using linked databases, using large healthcare systems that have electronic medical records, understanding that there are issues of confounding by indication and other things that will be limitations in understanding safety signals. But I am very concerned about after-market surveillance and believe that at least at this point, a registry is going to be necessary, or some type of a observational design to understand the safety signal.

DR. O'NEIL: Dr. McAlindon.

DR. McALINDON: Since it is already proposed to do some sort of educational intervention with the clinicians, it would be a fairly simple step to have all those clinicians registered and have them keep records on the patients to whom they administer the intervention with, and undertaking that the patients will be contacted. They don't necessarily have to be seen in the office, but they could be contacted by a mail survey so that we could get more complete data.

DR. O'NEIL: Dr. Haque.

DR. HAQUE: I agree with Dr. Weisman's point that the best way to collect the data and really see what's happening all the way across the board would be a mandatory registry. But I do think that's a little bit of an unfair burden on this particular drug when we don't do it for so many other drugs that also have very high-risk profiles.

And I do think that a broad capture type of study would be a reasonable way to try to alleviate some of our concerns that way, although it won't be perfect. And once again, I would put a plug in for

some kind of standardized consent form so patients really do have an idea of what even to look for, because, as was mentioned before, if you've spent the past six years holding your finger down like this and suddenly you're stuck out here and can't bend it down again, you may not be unhappy with that, but it doesn't help us if you don't report it.

So patients do need to know really critically what to look for, and so I do think that some kind of standardized consent form that informs them of what their bad outcomes would be would be very helpful.

DR. O'NEIL: Dr. McAlindon.

DR. McALINDON: I would counsel against trying to impose a standardized consent form, because institutions tend to have or view themselves as having autonomy. You could promulgate a template, perhaps, that they could adapt, but I don't see how you could operate a single design consent form across the country.

DR. O'NEIL: Dr. Swartz.

DR. SWARTZ: I'll disagree with that. In

plastic surgery circles, we do a certain broad range of operations but they're pretty standardized, including breast reductions, tummy tucks, those have -- the Society of Plastic Surgeons has a very nice informed consent form. It's not something -- it's something that it's a tool that you can use, and it's between the doctor and the patient. The hospital doesn't have to approve it. You don't even have to submit it to the hospitals. Most hospitals have their own individual consent forms that are non-specific.

But this way, you have -- you can assure that the information that's on that sheet is the information you want imparted, and that is always between the doctor and the patient to come to an understanding that they understand that information. But I think we as clinicians will need -- we can't manufacture this consent process de novo every time a patient comes in. So I would urge along with Dr. Haque that the sponsor provide a patient-friendly, full, informed consent that we can use.

DR. O'NEIL: Dr. Mazor.

DR. MAZOR: I just wanted to agree with what

Dr. Saag said earlier in terms of the potential value of using existing databases in some of the large health plans. It seems like a natural match for this that might give not a 100 percent of the information that one would hope for, but an awful lot of it and would -- a lot of these plans have patients who stay with them for many, many years, so you would lose some folks, but you would be able to get some of this longitudinal data on outcomes that you might not be expecting at this point. So it seems like something to consider in post-marketing studies.

DR. O'NEIL: Dr. Weisman.

DR. WEISMAN: Just to urge some caution here. I recently saw some data which was very interesting. It's unpublished but will be soon on follow-up of patients from a very, very large joint replacement registry, where they really examine the question of what are the complications of the patients that didn't come back to the doctors versus the ones that did. And it was exactly what you thought, that the complications were twice as frequent in the patients that did not come back for follow-up over the

same length of time, went to other doctors and so forth and so on. And this was well-documented.

I'm really concerned about the whole system of voluntary follow-up of these issues. And I think Ken's point is extremely important here, to understand that to get good safety data, we're going to need to be able to apply a very clean mind. As somebody once told me, the definition of epidemiology is a clean mind applied to dirty data. So we need to apply a very clean mind to be able to capture data out there in those observational cohorts, and I think he's given you the marching orders about the need to do that.

DR. O'NEIL: I think at this point, I'm left to ask the FDA if they have other questions or other issues that we have not discussed -- except that I do have one. I think we need to revisit the question that Dr. Hamilton rose, that IGE antibody may indeed be a significant problem as people come back for other procedures, other injections over time. And we certainly know that repeated exposure to any foreign substance, particularly in subcutaneous or mucosal sites, is going to induce IGE antibody in as efficient

way as we know how to do it as humans.

So I think we need to address whether it indeed would be important to either look back through the sera that may have been collected. I don't know if it was in the Phase 3 long-term open-label studies, and also to be very careful about post-marketing surveillance about allergic and other immunologic reactions. And I do -- although there has not yet been a problem with coagulation, I think we need to keep our mind's eye open to that possibility.

DR. DELCONTE: I'd like to ask Paul Chamberlain to comment, because we have done -- looked at our serum. We have previously looked at IGE in the earlier studies. We did not see a correlation, but Paul.

DR. CHAMERLAIN: Yes, thank you for the question. We really have poured back over the data from the earlier studies, and the dilemma for us is that there was no single systemic manifestation of immediate hypersensitivity even in the re-treated subjects into open-label studies. So we have no biological evidence of an IGE-mediated response.

And typically, it's the clinical manifestation that begins the diagnostic process of Type 1 hypersensitivity. And if systemic immediate hypersensitivity reactions were observed, one would do a skin test, an in vivo test, in favor of an in vitro test. The in vitro IGE test is very useful perhaps for a confirmatory analysis where there are clinical manifestations of potential Type 1 hypersensitivity.

But in the absence of Type 1 hypersensitivity, you have no clinical positive control for your in vitro IGE analysis. So it's a little bit of a chicken and egg situation. It's a dilemma. Without a clinical positive, you've nothing really to validate the biological sensitivity of your in vitro analyses. So you can chase a very, very sensitive bioanalytical method and perhaps pick up very weak signals, which have no biological relevance at all.

So this has really been a dilemma for Auxilium. Can I just refer to the -- actually a publication from Dr. Hamilton? And Dr. Hamilton did publish some data in some Peyronie's subjects with an

earlier version of AA4500, and of those 45 subjects tested in a radio binding test, only one out of 44 subjects generated a very, very weak positive in that assay system. But because the pretreatment sample was not tested in the same assay, it's impossible to ascribe that to a treatment-related effect. And moreover, there were no clinical manifestations in those subjects.

So taking all the data together, the Auxilium position is that it would not be worthwhile going back to retrospectively analyze IGE antibodies in isolation of no clinical manifestation.

DR. O'NEIL: So you would propose doing that only if people had systemic allergic reactions first?

DR. DELCONTE: Yes, that's correct.

DR. O'NEIL: I would just like to comment, as someone who did actually complete training in allergy, that I would be unwilling to let someone do an intradermal injection in my forearm of clostridium collagenase.

DR. DELCONTE: And we agree that skin testing is probably not clinically relevant as well.

DR. O'NEIL: So does the FDA have other issues they would like us to discuss or address?

DR. OKADA: No. But we would like to once again express our thanks to the panel for your participation today, and also for the very helpful discussion and advice.

DR. O'NEIL: Thank you, everyone. This meeting is now adjourned.

(Whereupon, at 2:55 p.m., the meeting was adjourned.)