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Quick Pulse

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FDA Advisory Panel Unanimously Recommends Approval of Auxilium's Xiaflex for Advanced Dupuytren's Disease

Gaithersburg, MD
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The FDA's Arthritis Advisory Committee voted unanimously (12 to 0) to recommend Auxilium Pharmaceuticals' Xiaflex (AA4500/collagenase clostridium histolyticum or CCH) for the treatment of advanced Dupuytren's disease. Xiaflex is a novel, first-in-class, orphan-designated biologic injectable for the non-surgical treatment of Dupuytren's contracture, a disorder caused by an abnormal buildup of collagen in the hands, eventually causing the fingers to bend and be unable to extend. The panel agreed that the benefits clearly outweighed any risks, and several members spoke of the compelling testimony of public witnesses who said that the procedure changed their lives.

The FDA's original target PDUFA (action) date was August 28, 2009, and the panel was supposed to meet over the summer. However, because the FDA wanted some hand surgeons on the panel and because of scheduling problems, the advisory committee meeting was moved to September. The FDA did not update the target PDUFA action date and probably will not do so, so a decision is expected soon.

The company also is conducting clinical trials of the drug to treat Peyronie's disease, a curving of the penis with a similar mechanism to that of Dupuytren's disease, and for frozen shoulder syndrome. The panel was quickly sold on the drug's efficacy but had concerns about the many side effects. There were several calls for a registry despite FDA officials implying that a registry will never happen. Who could do the procedure was a topic of discussion. The rheumatologists on the panel generally said that its use should be restricted to hand and orthopedic surgeons, but the hand surgeons on the panel argued that it would be impossible to restrict use of Xiaflex. The rheumatologists wanted more rigorous training and proof of training, but the hand surgeons agreed with the FDA reviewers that the proposed training was extremely thorough and rigorous.

Background

Auxilium Pharmaceuticals filed its Investigational New Drug (IND) application in October 1994. The dose was agreed on in 2001. Auxilium licensed the product in 2004 with an IND transfer. The Biologic License Application (BLA) was filed on February 27, 2009, and it was accepted with priority designation on April 28, 2009.

Dupuytren's disease is a condition characterized by progressive, fibrous thickening of the palmar fascia with the formulation of nodules and cords. Patients with advanced Dupuytren's disease develop a fixed flexion contracture of finger joints (Dupuytren's contracture), most commonly metacarpophalangeal and proximal interphalangeal joints, limiting the normal extension of their finger joints. Surgically cutting the cords is the current treatment but is not curative, and there is a high likelihood of recurrence. There are no approved non-surgical treatments for Dupuytren's contracture. Surgical treatment is recommended when the metacarpophalangeal joint contracture is more than 30 degrees or the proximal interphalangeal joint is more than 20 degrees. Current treatment options are:

- Fasciotomy, but recurrence is frequent.
- Fasciectomy, the current mainstay of treatment in the U.S.
- Dermofasciectomy.

An estimated 3%-6% of Caucasians, particularly those of Northern European descent, develop advanced Dupuytren's disease, usually after the age of 40. The cause is unknown, but it may be associated with certain biochemical factors within the involved fascia. Progression is unpredictable. Dupuytren's disease is bilateral in about half of patients and is progressive.

In the early stages of the disorder, myofibroblasts form, and nodules form in the palm. In the intermediate phase, myofibroblasts align along lines of tension, and joint contracture begins. Nodules usually form in the palm over the metacarpophalangeal joint. They are usually painless. Following nodule formation, cords, which are firm, rope-like structures, start in the palm and extend into the digits. As the cords shorten, contractures form. The ring finger is the most commonly affected. Etiology is not completely understood, but associations with Dupuytren's disease include genetic factors, tissue ischemia, trauma or manual labor, epilepsy, and alcoholism.

Clostridium histolyticum is a fixed-ratio mixture of clostridial type I and type II collagenase isolated from the culture medium of the gram-positive bacteria *Clostridium histolyticum* and developed as a non-surgical treatment for Dupuytren's contractures. The proteinases in Xiaflex hydrolyze native collagen. When injected into Dupuytren's cords, the postulated mechanism of action is local lysis of collagen resulting in enzymatic disruption of the cord, leading to a reduction in contracture and improvement in range of motion of the affected joint or joints.

The company's proposed indication for Xiaflex is for treatment of advanced Dupuytren's disease, defined as a progressive disease resulting in fixed flexion deformity (contracture) in one or several joints most commonly in the fourth and fifth fingers of the hand. Xiaflex is a new molecular entity and a first-in-class biologic. It comes as a sterile lyophilized powder in single use vials and is reconstituted in sterile diluents ($CaCl_2$ and NaCl).

The Auxilium Perspective

Auxilium Pharmaceuticals senior vice president Benjamin Del Tito Jr, PhD, told the panel that Xiaflex is safe and effective and provides the first non-surgical therapy for managing Dupuytren's disease. He said that Dupuytren's disease is a debilitating condition. Surgical therapies can straighten joints but have limitations including complexity, injury to other structures, risk of infection and scarring, prolonged recovery, require physical therapy, and re-operative risk. Dr. Del Tito told the panel that Xiaflex is well tolerated and safe.

- Efficacy was demonstrated in three placebo-controlled, double-blind studies. Each study met the primary endpoint ($p<0.001$).
- Xiaflex was well tolerated with broad exposure in 1,082 patients.
- Adverse events were mostly local, self-limiting, and confined to the treated extremity.

The proposed dose of Xiaflex is a 0.58 mg injection into the target cord, followed by a finger extension procedure about 24 hours later to facilitate disruption of the cord in patients who did not have spontaneous disruption, and up to two follow-up injections at four week intervals if necessary.

Efficacy

Auxilium chief medical officer Dr. Anthony DelConte described the company's clinical program. In 13 studies, 1,082 patients received at least one injection. There were three Phase III double-blind, placebo-controlled trials in a total of 407 patients, followed by an open-label extension. There were four open-label studies and other supportive studies.

All secondary endpoints were achieved in Study 1, including reduction in contracture to ≤5º, clinical improvement, percent change in contracture, time to reduction in contracture ≤5º, and change in range of motion.

Dr. DelConte said that the company is conducting a 2-5 year follow-up observational study to look at the durability of response in joints with measurable improvement (≥20º) in contracture after treatment. It will also assess the progression

Xiaflex Phase III Trials

Measurement	Xiaflex	Placebo	p-value
Study 1			
Number of patients	203	103	---
Primary endpoint: Correction to within 0-5° after last injection	64%	6.8%	<0.001
Study 2			
Number of patients	45	21	---
Primary endpoint: Correction to within 0-5° after last injection	44%	4.8%	<0.001
Study 3			
Number of patients	23	12	---
Primary endpoint: Correction to within 0-5° after last injection	91%	0%	<0.001

of the disease in joints that were not treated or did not have measurable improvement after treatment. In summary, he said that all the double-blind studies met the primary endpoint and that multiple secondary endpoints were achieved, including improvement in range of motion.

Safety

Dr. DelConte said that clinical data showed:

- Most frequent adverse events were confined to the treated extremity, were mild or moderate in intensity, and resolved before the next injection.
- Serious adverse events included tendon rupture/ligament injury risk.
- Routine labs/vital signs showed no clinically meaningful differences between the drug and placebo.
- Antibodies develop in nearly all subjects but do not appear to affect the safety profile.
- No events/signals were indicative of systemic anaphylaxis.

Dr. James Tursi, vice president of clinical affairs at Auxilium, told the panel that 87.6% of 1,082 patients in the trials completed at least one dose of the drug. Most common adverse events were peripheral edema (77%), contusion (54.5%), and injection site pain (40.9%). Fewer than 3% of adverse events were severe.

Adverse Events with Xiaflex

Adverse event	Xiaflex (n=1,082)
Non-fatal serious adverse events	8.5%
Edema, peripheral	77%
Contusion	54.5%
Injection site pain	40.9%
Tendon rupture/ligament damage	4 patients

Nine subjects had a total of 10 serious adverse events which were considered treatment-related. The most common serious adverse events were ligament injury and flexor tendon rupture, followed by complex regional pain syndrome, Boutonniere deformity, deep vein thrombosis, sensory disturbance, Dupuytren's contracture, and tendonitis.

Dr. Tursi said that immunogenicity data showed:

- No consistent pattern between adverse event rates and increasing antibody titers in the rate of adverse events, severity of adverse events, duration of adverse events, or systemic anaphylactic reactions.
- Adverse event severity did not correlate with antibody titer.
- The duration of adverse events did not correlate with subsequent injections and increasing antibody titers.
- There were no systemic anaphylactic reactions.

Although virtually 100% of subjects created antibodies, antibodies do not appear to affect safety. Dr. Tursi said that although antibody titers increase with increasing injections, there was no consistent pattern of increasing adverse event rates with subsequent injections. He said the profile was consistent across the entire adverse event profile.

Risk management plan

Auxilium's risk assessment and risk minimization plan says that Xiaflex "should be administered by a healthcare professional experienced in the treatment" of Dupuytren's contracture. It also warns that injection of Xiaflex "into collagen containing structures may result in damage to those structures and possible permanent injury such as tendon rupture or ligament damage." The company's proposed patient information reads, "Rarely, damage or rupture of the tendon in the treated finger can occur. This may result in trouble bending your finger fully and may require surgical repair."

The company proposal for education for healthcare professionals is a CD-ROM and a manual for proper injection technique and finger extension procedure. In addition, physicians must sign a form that states that they understand the injection procedures and Xiaflex risks, including tendon rupture, and that they have viewed a Xiaflex video. If they don't sign the form, Xiaflex will not be provided.

The company's proposed risk management plan will look at:

- Potential risks: injection-related bleeding in subjects with coagulation disorders and allergic reactions.
- Tolerability and safety concerns, including localized reactions, tendon rupture, and ligament damage.

Dr. Tursi said that ligament damage and tendon ruptures are considered related to the effect of Xiaflex and will be a focus of the company's risk management plan, which will include product labeling, a physician training program, access management program, safety monitoring, and patient education.

1. **Labeling** for potential risks:
   - Exposure of collagen-containing structures to Xiaflex may result in damage to those structures, and possible permanent injury such as tendon rupture or ligament damage.
   - Risks of injection-related bleeding in subjects with coagulation disorders.
     - Caution with coagulation disorders.
     - Not recommended with concurrent anticoagulant medications.
     - Prophylactic low-dose aspirin use acceptable in clinical program.
   - Allergic reactions.
     - Contraindication with known hypersensitivity.
     - Prepare to address any allergic reactions.

- Because Xiaflex lyses collagen, care should be taken to avoid injecting into normal collagen-containing structures of the hand.

2. **Identified tolerability/safety concerns** include:
   - Localized reactions (common and expected). Most common include peripheral edema, contusion, and injection site pain.
   - Mild or moderate with resolution before the next injection without intervention.
   - Physicians and patients should know what to expect from Xiaflex.
3. **Localized reactions** (risk management activities):
   - Product labeling.
     - Local reactions are identified.
     - Multiple cords should not be treated simultaneously.
     - One hand treated per session.
   - Physician training – include details of local reactions.
   - Patient product information – local reactions described.

Company officials said that intended users should be physicians experienced in the diagnosis and management of Dupuytren's disease, including hand surgeons, orthopedic surgeons, plastic surgeons, general surgeons with a hand focus, and rheumatologists. Dr. Tursi said that the company's proposed physician training – a video and a manual – will be broader in scope and content than that used in the clinical program. Doctors will be required to "attest to completion of the injection training video or manual" before receiving access to Xiaflex. He showed two clips from the video, and the procedure did not appear particularly complex. The hand manipulation clip included how the doctor "pops" the joint to get the finger straight.

THE FDA PERSPECTIVE

The FDA's reviewers said that Xiaflex works, but that almost all patients had adverse events, though most were not considered serious.

FDA medical officer Dr. Eric Brodsky of the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP), Center for Drug Evaluation and Research (CDER), Office of New Drugs (OND), told the panel that Xiaflex worked in the two biggest trials, Study 57 (308 treated U.S. patients) and Study 59 (66 Australian patients), which he said served as the primary support for the safety and efficacy of Xiaflex.

Dr. Brodsky concluded:

- **Efficacy:** Results from controlled trials demonstrate a statistically significant increase in the proportion of patients achieving almost complete contracture reduction when treated with Xiaflex vs. placebo. Eighty-five percent of Xiaflex patients had ≥50% improvement in finger flexibility after up to three injections.
- **Safety:** Xiaflex injection was associated with twice as many adverse events than placebo, with most being local reactions. Serious adverse events, including tendon ruptures, were uncommon.
- **Special consideration:** Clinical trial results may represent a "best-case" scenario where the investigators performing injections had extensive professional training and were highly trained in Xiaflex injection and finger extension procedures.

Efficacy

The primary efficacy endpoint for the pivotal trials (Studies 57 and 59) and the supportive trials (Studies 03, 53, 51, and 02) was the proportion of patients who achieved a reduction of the contracture of the primary joint (either metacarpophalangeal or proximal interphalangeal) to 0-5° at 30 days after the last injection (clinical success). FDA reviewers said, "A numerical and statistically significant greater proportion of (Xiaflex)-treated patients compared to placebo-treated patients achieved clinical success after up to three injections" in the two pivotal

FDA View of Efficacy with Xiaflex in Pivotal Trials

Measurement	Study 57 (U.S.)		Study 59 (Australia)	
	Xiaflex 0.58 mg (n=203)	Placebo (n=103)	Xiaflex 0.58 mg (n=45)	Placebo (n=21)
Primary endpoint: Patients with clinical success (reduction of contracture of the primary joint)	64%	7%	44%	5%
Absolute difference	57%	---	39%	---
Secondary endpoint: Degree of contracture change from baseline at 30 days after last injection	79%	9%	71%	14%
Range of motion change from baseline 30 days after injection	36	4	35	8

trials. For the Xiaflex-treated patients, the mean number of injections required for clinical success was 1.7.

The FDA reviewers said that after up to three injections, Xiaflex treatment resulted in a greater decrease in the mean percent change from baseline in the contracture degree of the primary joint (metacarpophalangeal and proximal inter-phalangeal). Results for the endpoint when subgrouped by primary joint type were consistent with the overall results supporting a treatment benefit of CCH treatment in the change in degree of contracture.

After up to three injections, Xiaflex-treated patients in the U.S. trial "showed a significantly greater increase in the proportion of patients with ≥50% reduction in contracture from baseline compared to placebo-treated patients, 78% vs. 14%."

Recurrence of contracture was defined as an increase in contracture of ≥20° associated with the presence of a palpable cord. In 830 Xiaflex-treated cords that achieved clinical success, 4% had contracture recurrence. The mean follow-up period after clinical success was 7.4 months. Twenty-three percent of the recurrences occurred within three months of follow-up, and 50% occurred between three and six months of follow-up after clinical success.

Safety

Pooled safety data showed that almost all Xiaflex-treated patients had an adverse event and that a greater proportion had an adverse event compared to placebo-treated patients. The overwhelming majority of the adverse events were local reactions at the injection site, and the most common – edema, contusion, injection site hemorrhage, and pain – were likely related to Xiaflex. There were no severe allergic reactions requiring hospitalization or associated with respiratory compromise or end-organ dysfunction. The FDA said that 125 patients would need Xiaflex treatment for one patient to have a tendon rupture, and 85 would need treatment to have a serious adverse event other than a tendon rupture.

FDA reviewers said that there were seven deaths in Xiaflex-treated patients in the complete clinical development program. Two deaths occurred in extended follow-up from an earlier, academic pilot study. In an early dose-ranging clinical study, there were no deaths in the placebo-treated or the Xiaflex-treated patients who received either 0.145 mg or 0.29 mg, but exposure periods were brief. The FDA reviewers said, "The reported causes of death were consistent with the underlying patient populations and their comorbidities."

Major Safety Results in Double-Blind, Placebo-Controlled Portions of Pooled Pivotal Trials through Day 90

Measurement	Xiaflex 0.58 mg n=249	Placebo n=125
Deaths	0	0
Any serious adverse event	3%	1%
Serious adverse events involving the injected extremity	2%	0
Any delayed adverse event	1%	0
Any adverse event	98%	49%
Specific adverse events		
Tendon rupture	1%	0
Complex regional pain syndrome	1%	0
Ligament disorder	1%	0
Ligament injury	1%	0
Spine fusion surgery	1%	0
Panic attack	1%	0
Acute cholecystitis	0	1%
Edema involving the extremity	73%	5%
Contusion	55%	3%
Injection site hemorrhage	38%	3%
Pain in extremity	35%	5%
Injection site pain	33%	6%
Injection site swelling	24%	6%
Tenderness	24%	0
Ecchymosis	20%	1%
Lymphadenopathy	12%	0
Pruritis	11%	1%
Skin laceration	9%	0
Lymph node pain	8%	0
Axillary pain	6%	0
Erythema	6%	0
Injection site pruritis	5%	0

Serious Adverse Events Involving the Injected Extremity in the Controlled and Uncontrolled Xiaflex Studies

Study	Serious adverse event of the injected extremity	Days between last Xiaflex injection and adverse event	Number of injections into cord	Treatment/ Outcome
In the 90-day controlled portions of the studies				
57	Tendon ruptures	4 days	3	Surgery
57	Tendon ruptures	7 days	1	Surgery
57	Complex regional pain syndrome	13 days	1	Steroids, pregabalin, and hand therapy
57	Ligament disorder	20 days	3	Event ongoing
58	Flexor pulley ruptures	43 days	2	Surgery
In the open-label, uncontrolled portions of the studies				
55	Tendon rupture	≤7 days	1	Surgery
59	Sensory abnormality of left hand	13 days	2	Resolved
54	Fracture of the tip of the right second finger with a ligament tear	14 days	1	Recovered without surgery
58	Boutonniere deformity	28 days	1	Splint, ongoing
56	Elective amputation of the right fifth finger	103 days	1	Surgery

There were 11 serious adverse events involving the injected extremity in the controlled and uncontrolled portions of the 12 submitted Xiaflex studies of 1,082 patients (a total of 2,630 injections). Three were tendon ruptures, and one was a flexor pulley rupture. They appeared to be related to study treatment. The patient who had her right fifth finger amputated had received a Xiaflex-injection near the fifth metacarpophalangeal joint, but she also had a severe untreated contracture near the fifth proximal interphalangeal joint which rendered the digit non-functional. She later injured the fifth digit in an unrelated traumatic event, resulting in the recommendation for elective amputation.

Data suggested that mild allergic reactions occur at an increased rate in the Xiaflex-treated patients, and the likelihood increases with successive injections. However, severe reactions – such as those requiring hospitalization or adrenergic agents or those associated with respiratory compromise, hypotension, or associated symptoms of end-organ dysfunction – were not observed. Two cases of hives and several rashes were reported in the 12 submitted studies. A greater proportion of Xiaflex-treated patients had pruritis adverse events after up to three injections vs. placebo-treated patients. The FDA reviewers said, "Overall, these data suggest that CCH (Xiaflex) is an allergen, as might be expected for a product comprising foreign proteins, but do not suggest severe allergies are likely with typical clinical exposures."

Immunogenicity

- 86% of patients had positive antibodies to AUX-1 and/or AUX-2 after the first Xiaflex injection.
- 100% of patients had antibodies to AUX-1 and AUX-2 after the fourth Xiaflex injection.
- No significant difference was seen in the proportion of Xiaflex-treated patients with positive or negative neutralizing antibodies to AUX-1 or AUX-2 who achieved the primary endpoint.

Who performed the procedure

The FDA did a subgroup analysis by expertise of investigators who performed the injections and found that investigators achieved similar results for the primary endpoint regardless of their specialty. However, the FDA said that no definitive conclusions could be drawn because of the limited number of doctors who were not hand surgeons.

Most of the physicians performing the injections in the clinical studies were surgeons, both hand surgeons and orthopedic surgeons. In Study 29, a subgroup of rheumatologists injected the medication. The FDA reviewers said, "Although rheumatologists performed injections in a limited number of patients, (they) achieved similar results for the primary efficacy endpoint as the hand surgeons, 45% vs. 44%."

Training

The FDA's Dr. Brodsky said that no hands-on training such as simulations were performed in preparation for the trials, and none is considered for training if Xiaflex is approved.

The FDA reviewers said that while investigators in the pivotal trials received product-specific training in injection procedures including manuals, DVDs, workshops, and meetings, there were questions about how much professional and product-specific training may be required if Xiaflex is approved. The training sessions did not include simulations. Principal investigators trained all sub-investigators in procedures. FDA reviewers said, "This raises questions regarding whether healthcare professionals without surgical training would have similar efficacy and safety results after having had similar product-related training and instruction."

Risk:Benefit Overview after ≤3 Intra-Cord Injections

Measurement	Xiaflex	Placebo	Number needed to treat (NNT)
Possible benefit			
Proportion of patients who had a contracture reduction 0-5° after ≤3 injections	60%	6%	~ 2
Proportion of patients with ≥50% contracture reduction from baseline after ≤3 injections	83%	12%	~ 1
Possible risk			
Local adverse events	95%	26%	~ 1
Serious adverse events involving the treated extremity	2%	0	~ 50
Tendon rupture	1%	0	~ 125

Panel Questions for Auxilium and the FDA

Questions focused on **adverse events**, including tendon rupture, how extensive the **training** should be, which **physicians** should perform the procedure, and the company's **risk management plan**.

Adverse events

Asked about the deep vein thrombosis, Auxilium's Dr. Tursi said that the event did not relate to the drug. The patient was a 62-year-old Australian who drove two to three hours in each direction to get his injections. Two days after an injection he had left knee and calf pain. Doppler revealed single lower extremity thrombosis – superficial and deep. Dr. Tursi said that AUX-1 and AUX-2 are effective at cleaving collagen into small fragments.

Asked how the tendon ruptures occurred, Dr. Tursi said that there is no way to determine what happened to cause the ruptures, "Whether it was directly injected into the tendon or the proximity of the tendon is unknown. It is a key focus of our risk management plan."

Panel chair Dr. Kathleen O'Neil, a pediatric rheumatologist from the University of Oklahoma College of Medicine, asked if the company had thought about ultrasound for guidance, and a hand surgeon speaking for the company said that it is very easy to get to the cord, but the problem may result from going through the cord. A hand surgeon and lead investigator said, "Once the doctor knew that there was a possibility of tendon rupture, he became more aware of the possibility. If he had patients in which he couldn't feel the cord, he stopped giving the shot. There were no nerve or artery injuries in the trials."

The surgeon admitted that one of the tendon ruptures was in one of his own patients, "He had previously had surgery on his other hand and had been out of work for six months due to a flare. He went back to work and was moving a pallet when he had the tendon rupture. In one of the other tendon ruptures, they intervened more quickly and did a tendon reconstruction procedure, followed by a tendon graft procedure. When ruptures are due to collagenase, it would not be directly repairable, but you might have to consider reconstruction options."

Asked what happened in the four cases of tendon rupture and ligament injury, the hand surgeon, speaking for the company, said, "The doctor needs to pay attention if they're going to do a new procedure…This is a new tool. I had no experience with collagenase prior to the trial. Feeling that resistance of injecting into the cord was a new experience, but you knew it right away. If you weren't in the cord, you knew immediately that you were out of the cord, and you needed to stop the injection. The important thing to highlight is that...we get physicians who are knowledgeable about the condition and give it the due that it requires."

A rheumatologist speaking for the company said that tendon ruptures did not occur with any of the rheumatologists doing the injections, "The first injection was certainly different, and it was much more comfortable after that…When we got our first dose of a biologic that was intravenous, we weren't set up with IV poles, and there were no videos to help us give those biologic drugs…It (Xiaflex) is a potent drug, certainly, but we deal with potent drugs every day. The side effects are based on physicians calling in and making the description or complaint of what happened, and Auxilium has it set up correctly."

Asked if the FDA found data to look at the overall risk of tendon rupture following steroid injection, which is something doctors do daily, and whether who did the injection mediated part of that risk, an FDA scientist answered that the FDA did not perform a literature search to see what the going rate of tendon ruptures with steroid injections would be, but it was a useful suggestion. As far as the details of who injected the patients who experienced the tendon ruptures, all of them were injected by hand surgeons, but it was mostly hand surgeons doing the procedures.

Asked how the company plans to record all adverse events, Dr. Tursi presented the targeted pharmacovigilance plan. He said, "Things will include a safety hotline, and an aggregate safety review will be monthly during the first year. There will also be a quarterly review during Years 2-5. We will adjust our training program during the course of the plan."

Asked about other adverse events, the lead investigator said that he had a few patients come back with irritation, and he noticed that some patients had a thinned tendon, "It's difficult to capture every patient and babysit them. But we can make them aware of what to look out for, to tell physicians what to look out for, and to call if there is a problem."

The science

Asked about collagenases, in particular the complement system, which is a series of collagenases that act together and have broad complications when allowed to proceed uninhibited in the body, a toxicologist for the company answered, "We haven't evaluated these directly in animal studies because there is an extensive literature base...There is no basis that collagenase directly…interferes with the thrombin pathways…We haven't seen any indication of that in the animal studies...There is no evidence that the product itself interferes with those pathways."

Asked about classes of IgG antibodies, a company scientist addressed the assay specifics, "We were measuring a total antibody regardless of class, so that would be substantially IgG, and we probably wouldn't detect IgE, but it would be measured in the assay. In terms of the IgE question, there was a series of treatments in one study and then rolled into another study. That's where you might expect to see exacerbation of immune (problems). The data in the first study (Study 57) showed increasing titers of anti-AUX-1 and anti-AUX-2 antibodies. Subjects then rolled up into an open-label study (Study 58), and from the first injection the titers were at baseline level but rebounded on the second, third, fourth, and fifth injections. This is what (one) would expect to see." Dr. Tursi added, "The antibody titers were higher in that study…The antibody event profile shows no difference or, if anything, an improvement in the adverse event profile…There are no differences if not improvements...suggesting that there does not appear to be any risk consistent with duration of injection. As for subjects in the 5-6 year range in intervals, there was no difference in the profiles even if there were 10 years between injections."

Asked if there was a complete rollover of patients from Study 57 into Study 58, Auxilium's Dr. DelConte said that only 6 out of 308 patients did not roll over.

Who should perform the procedure

While hand surgeons generally thought that any doctor with hand experience could do the procedure, the rheumatologists and non-surgeons fought against that idea, arguing for greater oversight over doctors wanting to do the procedure. The hand surgeons said that it would be nearly impossible to try to restrict who could do the procedure.

Asked how much experience the researchers had, Dr. DelConte said that academic medical centers, large research clinics, and private practices were all used in the studies, and experience ranged from one year to more than 20 years of practice.

Asked by California rheumatologist Dr. Michael Weisman of Cedars-Sinai Medical Center if a great expertise in hand surgery would be needed considering the possible complications and the fact that many patients would require hand manipulation, which internists and rheumatologists are not used to doing, Dr. DelConte said, "We consider this a medical procedure." A company executive said that rheumatologists often do injections for joints and emphasized that the procedure is relatively straightforward and wouldn't be too difficult to teach or train to perform. A practicing rheumatologist speaking for the company said, "Rheumatologists inject trigger fingers, joints, and this was a different injection, almost a simpler injection in the sense that the cord is so different from other tissue. Joint manipulation is not something we do every day in clinical practice. It was a learning process. With the first patient, it was a fairly simple procedure. No disrespect to hand surgeons, but I do think that we have the experience to do the manipulation. It did not require a specific amount of excess training. The video was a completely different video from the one we saw as an investigator, and the training is much easier in this video. Yes, I think we can do the injection. Second, the manipulation I do believe can be done."

Asked by Dr. Weisman who would be on the proposed panel that would oversee physicians and whether that panel would be accountable to review, Dr. Tursi described the company's screening process in which physicians fill out a form stating their specialty, "The access management program's intent is to provide access to those physicians best suited to ultimately use the product. An important component is the attestation – if it's within one of the specialties the company noted, the process would move automatically. If the doctor describes himself as 'other,' the safety group would look at whether to give access to that physician."

Dr. Weisman asked the FDA, "Is there sufficient concern you have that, given the safety and the risk associated with this drug, going forward this should be limited to hand surgeons as defined – and we can define what a hand surgeon is – only? Is that what your concern is?" An FDA official responded, "That's the crux of the issue. We have nice study results, and they are limited in terms of the expertise of the investigators."

Asked by a rheumatologist for the definition of a hand surgeon – although the FDA was not asking for the panel's input on which doctors can do the procedure – panel member Dr. Saul Kaplan, a hand surgeon from Virginia, said that the current definition is a doctor board-certified in plastic surgery, general surgery, or orthopedic surgery who has done a one-year fellowship in hand surgery. He added, "I'm not sure that we should exclude rheumatologists as a whole in this conversation."

Panel member Dr. Kenneth Saag, an immunologist and rheumatologist from the University of Alabama at Birmingham, said that he shared "the concern that certain types of providers may have less experience…I do believe that a certain level of training and acquiring sufficient knowledge and skills is necessary to safely perform a procedure that has some risk." An FDA official said, "I'm not aware of any test ...(to measure proficiency in training)." Dr. Bob Rappaport, director of the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products, CDER, told the panel, "We don't regulate surgical procedures."

Panel member Dr. William Swartz, a Pennsylvania plastic surgeon who sits on the American Board of Plastic Surgery and specializes in hand surgery, said, "The facts of the matter on the ground are that there are many people who do hand surgery who are not board-certified…and I'm not aware of many hospitals that require that certificate. If that were the case, we'd have a woeful dearth of people able to treat hand injuries on a regular basis. So, in my hospital you don't have to be certified in hand surgery. You do have to have a certificate and have experience in hand surgery in order to be accepted by the hospital (for) privileges. In an outpatient clinical setting there is no regulation…other than a surgical center/facility. And that has to be kept in mind when we consider who's going to treat these patients. My personal opinion is that anyone who has experience treating hand patients and treats them regularly should be allowed to treat them. An example would be a rural doctor…He'll have the maturity to decide his risk profile and will or will not use it based on that, and this is where it's going to come down to." Two FDA officials nodded their heads in agreement.

Panel member Dr. Mustafa Haque, a hand surgeon from Georgetown University Hospital who is also in private practice, agreed with Dr. Swartz, "A person who does several injections a month in trigger fingers would have the dexterity and feel of how to give this injection, and we shouldn't exclude them based on some labeling with their training or background." In terms of devices, he said, "Prior to getting approval to do it by the company, I had to do a hands-on course where I had to do cadaver training…actually had to perform the procedure and people were watching it. That is an additional burden on the provider and the company marketing the product, and in this situation it's hard to do. It's going to be an on-the-job situation."

A rheumatologist on the panel, arguing for restrictions on who could do the procedure, asked, "What are our provider resources? We want to make sure that the most experienced providers deliver this care, but we also want patients to have access to this care. We're calling it an orphan disease…It sounds as if some of the answer might be providers who do a lot of these kinds of procedures. Something we can't forget is that I don't know what the reimbursement will be, but we know that sometimes there's a bias to do any procedures if reimbursement is high. There might be some abuse of this procedure by some people who aren't as experienced. But we

have to be sensitive to the fact that there needs to be some restriction on this."

Training

While the panel rheumatologists said that they wanted better training materials and even a test to make sure that those looking at the materials understood the procedure, the panel hand surgeons and the FDA reviewers said that the proposed training is already extremely thorough.

Asked about the training materials, Auxilium's Dr. Tursi told the panel that the company is proposing more training than what study investigators received. It includes improved preparation, injection technique, and finger extension, adverse event reporting information, and important safety information. All adverse events ≥5% will be reported.

Asked how, just by looking at the training video, "*one could be sure that there is adequate knowledge and experience gained to avoid a significant learning curve*," Dr. Tursi said, "We went to the physicians to ask what they prefer, based on their understanding of the knowledge and disease, and the answer came back just from hand surgeons but generally (it was a training video)."

The consumer representative said that she liked the company's presentation and called the video a "wonderful tool." She asked if there is a slide about exclusion of patient populations. A company executive said that key exclusion criteria include patients with bleeding disorders or recent stroke, with other disorders affecting the hand, and a few others. He said that patients with rheumatoid arthritis were excluded in the trials.

Dr. Weisman, a rheumatologist, said, "We need to focus away from the food chain issue and talk about what really is the crux of the matter: the discrepancy between what was done in the clinical trial and what is being proposed for safety monitoring and safety assurance. Now, the sponsor has told us that they have improved on that imbalance, and they are better than what was during the study, and the FDA has reviewed this and said that there are some gaps between what the sponsor is proposing and what had gone on during the trial. Let's focus on those gaps. Have they improved on this or do the gaps still remain between what was done in the trials and what's being proposed going forward? And this is not just an injection; this is a procedure that involves manipulation following the injection and a recognition that a tendon might have ruptured or a ligament might have ruptured, which requires some definite cerebral expertise and being able to sort it out."

An FDA scientist said, "The FDA reviewed the revised training manual and DVD, and we concur with the sponsor that they have made some significant improvements, and so they are fairly comprehensive. The situation is still somewhat questionable in terms of how much hands-on and person-to-person training went on during the trials, and that's not so clear. They say they will have liaisons available; we're not sure what those liaisons would be, whether any clinicians could use them. Those we're not clear on."

An Alabama immunologist on the panel asked for some guidance from the FDA about the possibilities, "Certainly what the sponsor is presenting is reasonable, but is it enough? Is this sufficient?" Dr. Rappaport told the panel, "We're going to turn it back to you. What do you think about whether the training is adequate, whether the trainers have to be from certain groups? There's no way to know that despite 10 years of expensive clinical trials, and in the meantime we have patients in need."

The panel chair asked what happened when the company changed the injection technique for the proximal interphalangeal joint, "Do we have any evidence whether that changed the outcome? Did the complication rate decline?" Auxilium's Dr. Tursi said that with the training reinforcement there was an improvement. Before the training reinforcement, two tendon ruptures occurred in 734 injections (446 metacarpophalangeal and 288 proximal interphalangeal cords). After the training reinforcement, there was one tendon rupture out of 1,896 injections.

Indications and off-label use

Asked whether doing the procedure on patients with beginning Dupuytren's disease would be considered off-label, Dr. DelConte said, "We did a subanalysis – in the two large multicenter studies – and the metacarpophalangeal joints generally do better than the proximal interphalangeal joints, and joints generally of low severity tend to do better than joints of high severity…About a quarter of patients with more than 40° severity will achieve the endpoint of 0-5°. Proximal interphalangeal joints, particularly of high severity, do not tend to correct as well…As to where this would be used, we would not be seeking an indication specifically for nodules – only where there is a contracture, and in most cases patients wouldn't be coming in unless they had some sort of functional disability as well. We do propose looking at a follow-up of not only joints that have been treated but joints that have not received therapy to look at progression, so we'll gain some information on the natural history of the disease."

Another panel member concerned about off-label use asked if the company has data on recurrence of Dupuytren's disease that it has not shared with the panel. The panel member said that data from a follow-up study presented at the recent hand conference in San Francisco showed, "Six out of eight patients had recurrence of Dupuytren's disease, and in two situations the recurrence was worse than on original presentation. In four it was mild, and in two others it did not recur." A company executive answered that the durability of response was "30 recurrences out of 830 patients treated. The rates at one year are 6.7% in successfully treated joints. The average recurrence is 19%-22% in surgery patients. The follow-up study will take patients from current trials and will last 2-5 years. As for the eight patients from San Francisco, we realize that is a small number."

Asked about the company's recommendation to only inject one cord at a time since there are many patients with bilateral involvement, Dr. Tursi said that the recommendation would not be to inject more than one joint at a time. However, he added that some patients had two weeks or less between injections, and all subjects who had two injections at short intervals were successful.

Asked if a patient with prior surgery could get the procedure, Dr. Tursi said that patients with prior surgery were accepted into the trial. Response rates were 63.1% of patients without prior surgery vs. 59.4% of patients with prior surgery, "We looked to see if they had prior surgery in the same finger, and there was no overall difference."

Risk management plan

Asked if the company had a standardized consent form listing risks and benefits, Auxilium vice president Dr. Del Tito said that informed consent is not part of the risk management plan.

Asked if the panel could make suggestions about a registry instead of requiring a REMS (risk evaluation and mitigation strategy), the FDA's Dr. Rappaport said, "There is a whole range of possibilities." However, another FDA official said that registries are expensive and do not necessarily provide all the answers about safety.

Dr. Rappaport added, "I hear two questions there. One is what can we do under a REMS, and the other is maybe what is needed, or do we fully understand what will work in this situation or how to assess that. We don't know a lot yet about how REMS work. But as to whether we should be imposing (more) restrictions…we can require that only certain specialties are doing these procedures, or we can do nothing. Let's go back to the fact that we have over the last couple of years learned some new things about imposing restrictions, and you need to take the impact of imposing restrictions into consideration…The company has provided quite a restrictive plan. Whether it will work has yet to be seen, and one possibility is to let them take the responsibility to make sure that the right people are allowed to use the product, and then we can monitor over time to see if that is working. That's one option. The other thing is that we could have our own mandated restrictions, and we can fine people…In doing that we impose a large burden, and that's part of what's in the law. We have to consider how much of a burden we are placing on the healthcare system. There's a huge burden and a huge risk. There isn't any medication out there that doesn't have risks… If this doesn't work, we can always step in later. If we see problems with tendon rupture later…we still have the authority to step in and add additional restrictions."

Dr. Curtis Rosebraugh, director of the FDA's Office of Evaluation II, said there are two flavors of registries, "We very seldom have had programs where we register every patient who gets treatment. It's very extreme for us to do that." Dr. Weisman answered that it works in Europe, "where we have gotten good data, in contrast to the U.S., where the data are not good." Dr. Rosebraugh responded, "That isn't something that we have done, and it would be one of the strictest REMS that we would put in place." Another FDA official said, "We do have post-marketing requirements, and we could ask for a large, simple trial and take all comers and follow them for a certain period. Something like that might be more feasible and less restrictive on the general public than a mandatory registry of all patients."

Non-responders

Asked about non-responders in the studies and if there are any clues about who should not be treated, Dr. DelConte said that there were some patients who didn't get down to 0-5° but where there was some improvement.

Asked if any patients went on to get surgery, the study investigator said that there were some who got operations after injections. He said he had one non-responder whom he took to surgery. The patient had a big, thick cord that did not break. Another patient had eight injections (three placebo followed by five Xiaflex). While the injection site was a little mushy, tissue planes were not obliterated. Of those patients or patients who didn't get the three injections, there often was no palpable cord.

PUBLIC HEARING

Five people treated with Xiaflex said that it changed their lives, and several got emotional talking about how they felt after getting the use of their hands back. A Johns Hopkins researcher warned of the possible consequences of long-term use.

Tom Fewell, a patient from Illinois, said that the procedure changed his life. Before the procedure, he couldn't shake hands, and it was a painful ordeal to put on gloves. He had two surgeries and one set of injections. He said that he had intense, 10-second cycles of pain during the hand manipulation. After three cycles of Xiaflex, he recovered use of his hands. He can now shake hands, clap, and put his hands in his pockets to retrieve his keys. His treatments ended 18 months ago, and the cords have not reappeared.

Rodney Van Sickle, a fire captain who has had Dupuytren's disease for about 12 years, said that three surgeries did not help, but that after three injections of Xiaflex, his left hand is finally straight. The disease runs in his family, including his sons. He urged the panel to recommend approval.

Karen Mercaldo, a 61-year-old patient, was diagnosed with Dupuytren's disease in 1996. She said that she could use her hand immediately after her first injection. Six years later, she still has the full use of both of her hands, and her symptoms have not returned.

Kenneth Nelson said that Xiaflex returned the quality of life that he lost more than 20 years ago. He called Xiaflex the "miracle in my life." His father had Dupuytren's disease, and his youngest son is beginning to get the signs. He urged the panel to recommend approval.

Bill Walker, a patient from Indianapolis, said that the drug changed his life totally. His Dupuytren's disease started in his 30s. After the first injection of Xiaflex, while watching TV, his hand spontaneously popped open. After one month the hand was almost normal, "Being included in the study changed my life."

Robert Hamilton, PhD, an immunologist at Johns Hopkins, said that his lab did the early immunogenicity studies. He said, "There are five classes of IgE antibodies, and one of my puzzles was not to see the breakdown into IgE and IgG. In our initial testing…we detected IgE antibodies in about a third of the individuals subjected to the studies. After repetitive injections, some of the levels arrived at levels of patients who have allergies and who have allergic reactions. We do not expect to see allergic reactions in the first three months of treatment. The Phase III clinical data support the notion that the first three injections are safe. So, up to three injections the clinical data support the safety. If they ever choose to come back for a second course of treatment, that's precisely where you are going to see the systemic reactions. If you license it, I suggest that you license it for a first course of treatment and request additional studies when patients come back four to six months after administration. Finally, you need to define what is a large, systemic reaction, and anybody who manifests those symptoms (should) get evaluated for IgE and IgG."

Panel Consideration of FDA Questions

The original first question for the panel asked if expertise in hand surgery or in injections of the hands is necessary, and if so, should it be stipulated. The company proposed that the procedure should be done by "healthcare professionals experienced in the treatment of Dupuytren's disease." The day of the panel, this question was dropped.

Question 1. Is the training proposed by the company adequate?
Rheumatologists said no, hand surgeons said yes.

Although the first question about who should do the procedure was dropped on the day of the panel, the panel spent a great deal of time discussing the subject. The rheumatologists generally said that only hand surgeons and orthopedic surgeons familiar with Dupuytren's disease and hand problems should do the procedure. The hand surgeons and orthopedic surgeons said that access to the drug could and should not be restricted. The rheumatologists also came down on the side of more extensive and rigorous training, while the hand surgeons agreed with the FDA reviewers that the proposed training was rigorous enough.

Panel comments included:

- *Dr. Weisman, rheumatologist:* "Restricting the process to hand surgeons would be too restrictive. However, we don't know whether it will work with unrestricted individuals, and that would be too loose. What really fits the ideal to me is the way to do risk management would be a mandatory registry. This would answer…concerns of how are we going to know whether the folks who get the procedure are monitored…It's only after years of concern that now we're getting to the point where Congress is mandating registries of drugs…Voluntary registries have not been very useful. I understand the onerous issue of having to maintain it, but that could be an issue of negotiation between you (the FDA) and the sponsors. But I think that taking it up to that level should be considered by the panel…We've heard there is a low rate of complications, but when it occurs, it's quite severe, and if a rheumatologist does one of those, they'll really remember that…Also our colleagues have told us about the inadequacy of follow-ups, so a voluntary system of following these patients is inadequate. There has to be some improvement in that."
- *Patient representative:* "Is there a way to make sure that an untrained person does not give the drug?"
- *Dr. Saag, rheumatologist:* "It's time to look for new methods, maybe some sample, not a voluntary registry but some sample, of patients who might be treated by doctors with less historic expertise. That would be what I consider optimal. 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, manipulations of the hand, differentiating post-injection inflammation with infection, to be able to safely administer this product…Short of a more extensive training program, I would have reservations about the average rheumatologist administering this treatment…I feel strongly that while the training for hand surgeons and orthopedic surgeons (is sufficient), it is not adequate for rheumatologists. I'd suggest that most rheumatologists don't know where the A1 pulley is."
- *Dr. Nancy Olsen, an internist from the University of Texas Southwestern Medical School:* "The benefits look significant, and the risks look low, and after looking at the pictures and video, many of us could be trained to do this if we felt comfortable doing this. We do things in our office that are totally unregulated, so I think…it's something that would work and would be available to those who need it. I did like the idea of a registry, but I understand that it could be big. Maybe a sample registry to get unbiased sample (is an option) because I agree we need more data. But that shouldn't hold it (approval) up…A post-marketing trial would be useful."

- *Dr. Timothy McAlindon, chief of rheumatology at Tufts Medical Center in Boston:* "The data show that it's relatively safe. I think the point is to make it available to people. I'm concerned about restricting access. I think that the training proposed is likely adequate for clinicians who are used to doing...hand surgery. The registry would be a gold standard, but an alternative would be to have a registry of clinicians."

- *Dr. Kaplan, hand surgeon:* "It is an access issue. It requires up to three injections per joint per affected finger. People don't come in with one affected joint. They come back with multiple fingers, multiple hands, and they have to come back the next day. There are more visits with this procedure potentially than with surgery…In terms of follow-up and monitoring, it's difficult to get people with problems to come back to the office. I don't know how we're going to get people to come back who are doing well. I don't see how we can easily monitor this other than keeping in touch with the providers who do the actual work. As a surgeon, I'm familiar and comfortable with credentialing when it comes to operating room-based procedures. The concept of credentialing people to do things in their office is a world I'm neither familiar with nor comfortable with. People are injecting varicose veins, laser treatments, etc. The onus is on the physicians. The physicians who state they are comfortable in this area should be credited for deciding themselves what they're comfortable doing, the level of complications. A tendon rupture is awful; it's a disaster. Yet, at 3 per 1,100 I'm comfortable with it. It's less common than needle injury, less common than the range of infection…I think the training is ***more*** than adequate."

- *Kathleen Mazor, EdD, from the University of Massachusetts Medical School:* "One of my concerns is that… there be some sort of check that the physician had actually gone through (the training) and not just signed off."

- *Dr. Swartz, plastic/hand surgeon:* "It takes a long time to get more than 70 patients with Dupuytren's disease in most hand surgeons' practices. This is a pretty unusual patient even in a practicing hand surgeon's office. In a rheumatologist's office there aren't any patients with rheumatoid arthritis who have this disease. I've never seen one in 30 years. So, having said that, I think, first of all, that the training video DVD is adequate. In my opinion, the doctors who take care of these problems should be doctors who see these on a regular basis, are familiar with the disease. People who treat any disease entity should do so if they can manage the complications. Complications are rare but devastating. With information to the doctors and the patients, I'm okay with this training and the program that has been outlined by the company."

- *Dr. Haque, Maryland hand surgeon:* "I'm comfortable with the training regimen, but I want to make sure that the training is done." He suggested making the training on-line and for the doctor to pass a test. As far as healthcare professionals and the level of training, he said, "It seems to be a relatively simple procedure. The cords are fairly superficial, and…I don't know how many rheumatologists see patients with Dupuytren's disease. I was surprised when I heard some rheumatologists questioning the ability of rheumatologists to do the procedure. This isn't such a huge volume that people will get rich off of this procedure. If people are willing to sign up and see the DVD and take the test, they are probably qualified to do this."

- *Panel chair:* "When you asked how many rheumatologists see these patients, I'll tell you that as a pediatric rheumatologist I haven't seen one since I was a medical student…It does look like a fairly simple procedure. It looks like it has a low rate of severe complications. It is quite low in good hands, and hopefully the training and the registry of the trained practitioners will allow the company to maintain contact with the practitioners who are doing this and perhaps every few months by email or direct mail inquire if they have seen complications, thereby enhancing reporting of adverse events."

QUESTION 2. Should Auxilium's Xiaflex be approved for the treatment of patients with advanced Dupuytren's disease.
Unanimously YES (Yes 12, No 0)

Panel comments included:

- *Maryland hand surgeon:* "The overall safety profile looks good. It has a favorable risk:benefit profile."

- *Dr. Swartz, Pennsylvania plastic/hand surgeon:* "The benefit was very high, and I appreciated the patients' testimonials."

- *Dr. Kaplan, hand surgeon:* "It is another option. I want to be convinced that the long-term results are going to hold up enough to make it the mainstay of treatment. I'm worried that this, like surgery, will not be the ultimate answer."

- *Dr. McAlindon, Massachusetts rheumatologist:* "There is an acute need for non-surgical intervention for Dupuytren's disease. This product appears highly effective and has a safety profile that is better than the current surgical alternative."

- *Dr. Lenore Buckley, an internist/pediatrician at Virginia Commonwealth University:* "This is a treatment that offers patients who have significant disabilities significant benefits at an acceptable risk."

- *Panel chair:* "This is an effective and reasonably safe alternative to surgery and in some ways may be better than surgery."

- *Dr. Olsen, Texas internist:* "It satisfied an unmet need."

- *Dr. Saag, rheumatologist:* "Satisfactory risk:benefit ratio, and it fills an unmet need."

- *Dr. Weisman, rheumatologist:* "Yes, because of the evidence of two very well done trials and the significant unmet need."

QUESTION 3. What additional studies, if any, should be conducted post-approval to further assess the safety of the product.

No consensus but the panel wanted more safety data. The FDA and hand surgeons batted down the idea of a post-marketing registry.

Panel and FDA comments included:

- *Dr. Weisman, rheumatologist:* "I strongly recommend a registry. It will break new ground and represents to the FDA a somewhat onerous responsibility, but the voluntary registries that we've had so far in the U.S. have been inadequate."
- *FDA's Dr. Rosebraugh:* "REMS is still a work in progress. Mandatory enrollment of patients for this particular segment in reality means that in order for the drug to be used safely, you have to enroll the patient and make sure that the patient is followed. That's a little bit different than saying we need more data and we want to know more about the outcomes of patients. These are two different things, and I want to make sure that people understand it.
- *Dr. Kaplan, hand surgeon:* "The key is how many patients it would take to get a tendon rupture. It would take a lot of patients over a long period of time. A mandated registry would be onerous, and I am opposed to it. Instead, a post-marketing study would be useful…It is onerous to mandate doctors drag their patients back over an extended period of time." He said that several organizations and societies will be interested in following the patients.
- *FDA's Dr. Rappaport:* "We could require a post-marketing study, and we could talk about the best way to do that, whether we should include different specialties and all that. Beyond that, clinical trials give us better information than just about anything. But trying to tease out the information we'd like to get from a registry is going to be far more difficult than a controlled trial…(With a post-market registry) you still get into how you tease out the background noise from a registry. We can design a trial any way we want, broaden it for different populations at different risks."
- *Dr. Saag, rheumatologist:* "What would be good would be a large randomized clinical trial. If I saw the results from this, and the drug was approved, I wouldn't want the surgery. So, I think that we're stuck with an observational trial…I am very concerned about after-market surveillance and believe that a registry will be necessary."
- *Dr. McAlindon, Massachusetts rheumatologist:* "Since it's proposed to do some sort of educational intervention with the clinician, it could be useful to have a database of the clinicians and contact them by mail so we have access to their data."
- *Dr. Haque, Maryland hand surgeon:* "The best way to collect the data would be a mandatory registry, but that is a bit of an unfair burden on this drug when we don't do it for drugs that have high-risk profiles. A broad capture study might be a way to alleviate some of our concerns. I also want to plug some kind of standardized consent forms so patients do know what to look for."
- *Dr. Weisman, California rheumatologist:* "Just to urge some caution, I saw some unpublished data on follow-up of people in a joint replacement registry. They asked what were the complications of patients who came back for follow-up compared to those who didn't. I'm concerned about the whole system of voluntary follow-up. To get good safety data we're going to have to apply a very clean mind to be able to capture data out there in those observational cohorts, and we've given the marching orders about the need to do that."
- *Panel chair:* "We need to revisit the IgE antibody question. It may be a significant problem as people come back for other procedures, other injections over time. We certainly know that repeated exposure to any foreign substance can be problematic, and we need to address whether we need to look through the data that have been collected and be careful about post-marketing surveillance for allergic reactions. We also need to keep open about coagulation problems."

♦