FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE ANESTHETIC AND ANALGESIC

DRUG PRODUCTS ADVISORY COMMITTEE (AADPAC)

Friday, January 10, 2025

9:00 a.m. to 4:19 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

LaToya Bonner, PharmD, MBA

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE MEMBERS (Voting)

Brian T. Bateman, MD, MSc

(Chairperson)

Professor and Chair

Department of Anesthesiology, Perioperative, and Pain Medicine

By courtesy, Professor of Epidemiology and Population Health

Stanford University School of Medicine

Stanford, California

Mark C. Bicket, MD, PhD, FASA
Associate Professor, Department of Anesthesiology
Co-Director, Opioid Prescribing Engagement Network
University of Michigan
Ann Arbor, Michigan

Maryam Jowza, MD
Associate Professor of Anesthesiology and Pain Management
University of North Carolina-Chapel Hill
Chapel Hill, North Carolina

Maura S. McAuliffe, CRNA, MSN, MSNA, PhD, FAAN
Professor Emeritus, College of Nursing
Founding Director, Nurse Anesthesia Program
East Carolina University
Greenville, North Carolina

Mary Ellen McCann, MD, MPH

Associate Professor, Anesthesiology,
Care and Pain Medicine
Harvard Medical School
Boston Children's Hospital
Boston, Massachusetts

Michael Sprintz, DO, DFASAM

Medical Director, Intensive Outpatient Program
Ethos Behavioral Health Group
Houston, Texas
Founder, Sprintz Center for Pain and Recovery
The Woodlands, Texas
ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY
COMMITTEE MEMBER (Non-Voting)

Jeffrey B. Reich, MD

(Industry Representative)
CEO and Co-Founder
Sparian Biosciences
New York, New York

TEMPORARY MEMBERS (Voting)

D.J. Kennedy, MD

(via video conferencing platform)

Professor, Physical Medicine & Rehabilitation

Chair, Department of Physical Medicine & Rehabilitation

Vanderbilt University Medical Center

Nashville, Tennessee

John S. Kirkpatrick, MD, FAAOS, FAOA

Orthopaedic Surgical Services

Orlando VA Medical Center

Professor of Orthopedic Surgery

University of Central Florida College of Medicine

Orlando, Florida

Ariana M. Nelson, MD

Associate Professor, Department of Anesthesiology and Perioperative Medicine
University of California Irvine
Clinical Science Team, NASA Exploration Medical Capability Element
Irvine, California

Joseph P. O'Brien, MBA

(Patient Representative)
President, CEO & Patient
National Scoliosis Foundation
Stoughton, Massachusetts

Steven Schiff, MD, PhD, FACS

Harvey and Kate Cushing Professor of Neurosurgery
Vice Chair for Global Health, Department of Neurosurgery
Professor of Epidemiology
Department of Epidemiology of Microbial Diseases
Yale University
New Haven, Connecticut

Milan P. Stojanovic, MD

Assistant Professor of Anesthesiology

Harvard Medical School

Active Staff, Anesthesiology, Critical Care and Pain Medicine Service

VA Boston Healthcare

Boston, Massachusetts

Active Staff, Specialty and Acute Care Service

VA Bedford Healthcare

Bedford, Massachusetts

FDA PARTICIPANTS (Non-Voting)

Mary Thanh Hai, MD

Deputy Director for Clinical Science

Office of New Drugs (OND),

Center for Drug Evaluation and Research (CDER), FDA

Tina Doshi, MD, MHS

Associate Director for Therapeutic Review,

Chronic Pain

Division of Division of Anesthesiology,

Addiction Medicine, and Pain Medicine (DAAP)

Office of Neuroscience (ON), OND, CDER, FDA

Shaan Sudhakaran, MD

Medical Reviewer

DAAP, ON, OND, CDER, FDA

Sue-Jane Wang, PhD

Biometrics Deputy Division Director

Division of Biometrics I (DBI)

Office of Biostatistics (OB)

Office of Translational Sciences (OTS), CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

Introduction of Committee

DR. BATEMAN: Good morning and welcome. I'd first like to remind everyone to please mute your line when you're not speaking. All members of the public are reminded to silence their phones and other devices, and to otherwise refrain from disrupting the meeting. Loud talking or applause may make it difficult for meeting participants and observers to hear the proceedings. For media and press, the FDA press contact is Lauren-Jei McCarthy. Her email is currently displayed.

My name is Brian Bateman, and I will be chairing this meeting. I will now call the January 10, 2025 Anesthetic and Analgesic Drug Products Advisory Committee meeting to order. We'll start by going around the table and introduce ourselves by stating our names and affiliation. We will start with the FDA to my left and go around the table.

DR. THANH HAI: Good morning. I'm Mary Thanh Hai. I'm the Deputy Director for Office of New Drugs.

DR. DOSHI: Hi. I'm Tina Doshi. I'm the Associate Director for Therapeutic Review in the Division of Anesthesiology, Addiction Medicine, and Pain in the Office of New Drugs.

DR. SUDHAKARAN: My name is Shaan Sudhakaran. I am the medical reviewer, and I am in the same division.

DR. WANG: My name is Sue-Jane Wang. I'm the Deputy Division Director from the Division of Biometrics I, Office of Biostatistics, Office of Translational Sciences, CDER, FDA.

DR. KIRKPATRICK: Good morning. I'm John Kirkpatrick. I'm an Orthopedic and Spine Surgeon at the Orlando VA Medical Center and a Professor at University Central Florida College of Medicine.

DR. SPRINTZ: Hi. I'm Michael Sprintz. I'm boarded in anesthesia, addiction medicine, and pain medicine, and I'm the Medical Director of the Intensive Outpatient Program at Ethos Behavioral

Health, and Founder of Sprintz Center for Pain and Recovery.

DR. McCANN: Hi. Mary Ellen McCann from Boston. I'm a Professor of Anesthesiology at Harvard Medical School and work at Boston Children's Hospital.

DR. BATEMAN: So we'll now go to Dr. Kennedy.

DR. KENNEDY: D.J. Kennedy, Professor and Chair of PM&R at Vanderbilt University Medical Center in Nashville, Tennessee.

DR. STOJANOVIC: Milan Stojanovic from Boston Harvard Medical School, anesthesia; Assistant Professor at the VA via Boston as well; Editor-in-Chief for International Pain Medicine Journal.

CDR BONNER: Good morning. LaToya Bonner, DFO for this meeting, DACCM.

DR. BATEMAN: I'm Brian Bateman. I'm Professor and Chair of the Department of Anesthesiology, Perioperative, and Pain Medicine at Stanford.

DR. McAULIFFE: I'm Maura McAuliffe. I'm a nurse anesthetist from East Carolina University in Greenville, North Carolina. I teach anesthesia pharmacology in the College of Nursing in the School of Medicine.

MR. O'BRIEN: Good Morning. Joe O'Brien, President and CEO of the National Scoliosis Foundation, and I am the patient representative.

DR. BICKET: Good morning. My name is Mark Bicket. I'm an anesthesiologist and pain medicine specialist at the University of Michigan, where I'm an associate professor and direct the Overdose Prevention Engagement Network.

DR. SCHIFF: Steve Schiff. I'm a Professor of Neurosurgery at Yale, and I serve as the Vice Chair for Global Health in the department, and I'm also a Professor of Epidemiology there.

DR. JOWZA: Hi. I'm Maryam Jowza. I'm an anesthesiologist and pain physician, and I work at the University of North Carolina in Chapel Hill, where I am Associate Professor.

DR. NELSON: Ariana Nelson, Associate

Professor of Anesthesiology and Pain Medicine. I also have an appointment with NASA as part of their Exploration Medical Capability element.

DR. REICH: Jeffrey Reich. I'm the industry representative. I'm a CEO and Co-Founder of Sparian Biosciences, which is a biotech company based out of New York, spun out of Memorial Sloan Kettering with CNS-focused therapeutics. Prior to that, I was on faculty for many years in the Department of Neurology and Neuroscience at Weill Cornell, and ran the stroke and migraine service there.

DR. BATEMAN: For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this is a meeting that 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 chairperson. 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 public 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.

Commander Bonner will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

CDR BONNER: Thank you.

The Food and Drug Administration is convening today's meeting of the Anesthetic and Analgesic Drug Products Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, 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 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

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 U.S.C. 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 a special government employee's services outweighs their potential financial conflict of interest, or when the interest of a regular federal employee is

not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

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

Today's agenda involves discussion of BLA 761393, condoliase injection, submitted by Seikagaku Corporation for the proposed indication of the treatment of radicular leg pain associated with confirmed nerve root impingement caused by lumbar disc herniation in adults. This is a particular matters meeting during which specific matters related to SKK's BLA will be discussed.

Based on the agenda for today's meeting and all financial interest reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(1) to Dr. John Kirkpatrick. Dr. Kirkpatrick's waiver involves stock holdings in two competing firms. The aggregate market value of his financial interests in the common stocks of the two firms is between $25,000 and $50,000.

The waiver allows Dr. Kirkpatrick to participate fully in today's deliberations. FDA's reasons for issuing the waiver are described in the waiver documents, which are posted on FDA's website on the advisory committee meeting page, which can be found at www.fda.gov and by searching on January 10, 2025 AADPAC.

Copies of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be faxed via 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Dr. Jeffrey Reich is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Reich's role at this meeting is to represent industry in general and not any particular company. Dr. Reich is employed by Sparian Biosciences.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at

issue.

Thank you. I will now turn the meeting back over to our chair.

DR. BATEMAN: Thank you. We will now proceed with the FDA introductory remarks from Dr. Tina Doshi.

FDA Opening Remarks - Tina Doshi

DR. DOSHI: Thank you, Dr. Bateman.

Good morning and welcome to Dr. Bateman, members of the committee, and invited guests. My name is Tina Doshi. I'm the Associate Director for Therapeutic Review of Pain Medicine in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine in the Office of New Drugs.

Today, we will be discussing BLA 761393, condoliase for intradiscal injection. The applicant is Seikagaku, abbreviated SKK. SKK is seeking the indication of the treatment of radicular leg pain associated with confirmed nerve root impingement caused by lumbar disc herniation in adults. The mechanism of action of condoliase is similar to that of a product that has been

discontinued since 2001, so if approved, condoliase would represent the only product of this nature to be currently approved and marketed in the United States.

After the presentation and clarifying questions for the applicant, Dr. Shaan Sudhakaran will present the agency's clinical review and findings, and our team will take clarifying questions. Dr. Sudhakaran's presentation will set the foundation for the panel discussion later in the afternoon.

After clarifying questions to the agency and following a lunch break, we will resume with the open public hearing, during which we will hear from public speakers who have volunteered to share their input with the committee. After the open public hearing, I will give the charge to the committee, and Dr. Bateman will lead the discussion. As you listen to the presentations, I would like to ask all of you to keep in mind the discussion topics that are presented in the briefing document.

The condoliase program contains two positive

studies and one negative study. While the applicant has submitted substantial evidence of effectiveness, we would like to explore the extent to which the negative study may help inform the appropriate patient population for this product.

In addition, our review of the safety revealed two key concerns. First, due to the mechanism of action of the product, it causes mechanical changes to the intervertebral disc and adjacent tissues, which may lead to clinically relevant consequences in the short and long term. Second, this product is a foreign protein, and as such, it has the potential to cause hypersensitivity reactions. There are a number of severe cutaneous adverse reactions in the safety database.

Given these concerns and how the drug is intended to be administered, your discussion should also include comments about appropriate proceduralist qualifications and procedural setting. We hope that your discussions will enhance our perspective as we consider this new

biologic. We look forward to your discussions, and we sincerely appreciate all of you taking your time away from your busy schedules to assist us. Thank you.

DR. BATEMAN: Thank you Dr. Doshi.

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 advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with applicant, such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation 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 presentation, it will not preclude you from speaking.

We will now proceed with presentations from the sponsor.

Applicant Presentation - Jun Watanabe

MR. WATANABE: Good morning, Mr. Chairman, members of the advisory committee, and FDA. I'm Jun Watanabe, General Manager at Seikagaku North America Corporation, which we will refer to as SKK. Thank you for the opportunity to discuss condoliase for the treatment of radicular leg pain associated with radiologically-confirmed nerve root impingement caused by lumbar disc herniation. Condoliase was approved in Japan in 2018, and the latest estimate, 29,000 patients have been treated in the postmarketing setting.

We are so excited to share our data today to bring this important therapy to patients in the U.S. To provide some background, lumbar disc herniation, or LDH, is a result of protrusion or

prolapse of the nucleus pulposus and annulus fibrosus in the intervertebral disc. Ninety-five percent of herniation is LDH occurring in the L4-L5 or L5-S1 region of the spine. Once the disc has herniated, the leaking nucleus pulposus puts pressure directly on the spinal root, causing symptoms such as numbness and weakness in one or both legs or lower back pain.

First-line treatment of LDH is conservative and includes rest, physical therapy, oral medications, and steroid injections, among others. This kind of care is common across industrialized countries, including the U.S., Japan, and Europe, and results in a clinical response in most patients. Surgery is the next treatment option for 20 to 50 percent of patients who do not respond to conservative treatment, but there are no other approved options for people who are ineligible for surgery currently or do not consent to surgery.

Patients with leg pain due to nerve root impingement and inadequate response to conservative treatment need another treatment option.

Condoliase is a glycosaminoglycan, or GAG, degrading enzyme that reduces nerve root compression through lysis of the nucleus pulposus. The nucleus pulposus has a strong ability to hold water due to its GAG chains. It selectively degrades chondroitin sulfate and hyaluronic acid GAG chains. This loss of GAG chains decreases the water-holding capacity to the nucleus pulposus, decreasing its size and relieving disc pressure and compression on the spinal nerve root.

When condoliase is injected directly into the nucleus pulposus of the herniated intervertebral disc, it decreases the hernia volume. Since it is a treatment directly injected into the intervertebral disc, it does not require a general anesthetic and is less invasive than surgical treatment, and the decrease in the pressure is expected to reduce the leg pain caused by LDH.

Condoliase offers patients a non-surgical treatment option. Our proposed indication is for the treatment of radicular leg pain associated with

radiologically-confirmed nerve root impingement caused by lumbar disc herniation, or LDH, in adults. Condoliase is administered as a single-dose injection of 1.25 enzyme units injected into the nucleus pulposus of the herniated intervertebral disc.

Let me explain the clinical development program. The primary data set that supports a positive benefit-risk for condoliase consists of four phase 2 and 3 randomized-controlled trials. Studies 1021 and 1031 were conducted exclusively in Japan and resulted in the approval of condoliase in 2018 for the treatment of LDH with no sufficient improvement after conservative therapy. Studies 1131 and 1133 were conducted exclusively in the U.S.

All four studies are used to characterize an acceptable safety profile of condoliase together and are supported by the extensive postmarketing experience. The data supporting substantial evidence of effectiveness comes from Studies 1031 and 1133, demonstrating clinical meaningful

reduction in leg pain and improved functionality.

As per FDA questions number 1 and number 2, learnings from these studies and the negative study, 1131, inform us on the appropriate patient population for treatment with condoliase, and a detailed explanation will be presented in the efficacy section.

Through our clinical trials, we have characterized the labeled patient population to ensure that the most appropriate patients are treated with condoliase as requested by the FDA in question 2. First, the target patient population should have an inadequate response to conservative therapy. Importantly, patients must also have radiologically-confirmed visible nerve root impingement, understanding that patients without impingement are unlikely to benefit. These are also accompanied by established administration technique.

It is important to remember that condoliase will be administered by interventional pain specialists as you discuss for FDA question

number 4. Patients who are candidates for condoliase have already been enduring leg pain and restricted functionality for many weeks. By the time conservative therapy fails, patients will be managed by a specialist who is trained to do interventional pain medicine. These specialists have experience with spinal injections, which are well-established procedures. They will use fluoroscopic guidance during an injection procedure to increase precision.

Let me explain. C-arm fluoroscopic guidance allows continuous imaging to safely administer injection procedures like condoliase. This real-time imaging capability enables the treating doctor to insert the needle precisely and safely into a patient's intervertebral disc. The patient is positioned so that the disc space injected is parallel to the X-ray direction, and needle placement is confirmed throughout the procedure.

Before I pass off the presentation, I want to conclude with the key benefits and risks of condoliase for the treatment of radicular leg pain

associated with nerve impingement from herniation. Condoliase met the prespecified primary endpoint in two pivotal studies demonstrating significant and clinical meaningful improvement in both early and durable relief of worst leg pain compared with control. It also demonstrated a reduction in herniation volume and improvement in function at week 13 that persisted over time.

Overall, condoliase 1.25 dose units were well tolerated with an acceptable safety profile. A warning will however be included for hypersensitivity events, including anaphylaxis, which will be discussed later to address question number 5. The safety profile has been well characterized through clinical use and postmarketing surveillance in approximately 29,000 patients. These provide comfort with long-term safety implications and low potential for unintended consequences that will be discussed in question 3.

Here's our agenda for today's presentation. Next, Dr. Ajay Wasan will review the unmet need in

LDH, Joe Stauffer will then present the efficacy data, and Diane Martire will present the safety data. Tom Fuerst will discuss the disc-related imaging findings in our trials, and finally, Dr. Kee Kim will conclude with his clinical perspective on the condoliase data. We also have additional colleagues joining us today. All external experts have been compensated for their time and expenses related to this meeting.

Thank you, and I will now turn the presentation over to Dr. Wasan.

Applicant Presentation - Ajay Wasan

DR. WASAN: Thank you, and good morning. I am Ajay Wasan. I am a tenured Professor of Anesthesiology and Psychiatry at the University of Pittsburgh. I am also Vice Chair for Pain Medicine in the Department of Anesthesiology and Perioperative Medicine. I also co-direct the Center for Innovation in Pain Care, which focuses on the evaluation and treatments for acute and chronic pain. I am pleased to be here today to discuss the important unmet medical need for

additional treatment options in patients with lumbar disc herniation who have not responded to conservative measures.

Radicular pain is some of the most severe pain a person can experience, and it's often associated with great distress and suffering. Over the years, many potential therapies have tried, and failed, to provide patients with adequate relief of radicular pain, leaving a high unmet need for many patients I care for in my practice.

The patients that come to my office or seek care from a specialist have persistent leg pain that is unresponsive to the conservative standard of care. These patients are often experiencing worsening health and quality of life, as well as potential for longer term disability, increased caregiver burden, and lost days from work. Patients with uncontrolled pain self-select since they can no longer tolerate the pain or lost functionality.

Currently, there are no approved therapies in the United States for patients with lumbar disc

herniation that deliver long-term reductions in pain, improve functionality, and allow patients to avoid risks associated with surgery and long-term pharmacotherapy. Symptomatic lumbar disc herniation affects approximately 1 to 3 percent of the United States population. Males tend to be affected more frequently with a mean age of 30 to 50 years old. It is rare for LDH to occur in individuals younger than 20 or older than 65.

Certain populations, like those who are obese, are at an increased risk of herniations. These patients are more susceptible to complications and recurrent herniations compared to non-obese patients, which often requires them to undergo multiple revision surgeries.

The treatment progression journey is similar across industrialized countries. Patients typically present to their primary care physicians, and are then referred to a specialist who orders MRI and imaging studies. In the Japanese healthcare system, however, early in their presentation to the healthcare system, patients

often go directly to a hospital for outpatient care and imaging following their diagnosis. Most patients can then be effectively managed with conservative measures and do not need to progress to interventional treatments.

However, patients with continued symptoms, despite conservative therapy, will typically progress to epidural steroid injections, and those who do not respond to a first injection may or may not get multiple injections. The use of epidural steroid injections is more common in the United States compared to Japan. Patients with continuing symptoms after conservative treatment and epidural injections will be recommended for surgery, which is typically a discectomy.

Conservative treatment is often multimodal and personalized, depending on the severity of pain and response to treatment, with either one treatment at a time or more than one treatment at once such as medication and physical therapy. These treatments may also include traction therapy; spinal manipulation; chiropractic, exercise, and

physical therapy.

I may start a patient on anti-inflammatories and possibly a muscle relaxant as first steps, and then to neuropathic medications if needed. These are anticonvulsants and SNRIs such as duloxetine. When those don't provide accurate relief, I often consider a transforaminal or interlaminar epidural steroid injection, knowing that epidural injections may only provide temporary relief.

In general, conservative treatment can provide pain relief. According to the 2012 North American Spine Society, or NASS, guidelines, quote, "Most patients will improve independent of treatment. Disc herniation will often shrink/slash regress over time," unquote. These guidelines also state that, quote, "Many, but not all, articles have demonstrated a clinical improvement with decreased size of disc herniations." However, publications cite that 20 to 50 percent of patients do not respond to conservative treatments.

So, what happens to these patients? Patients who do not gain symptomatic relief with

conservative therapy have limited options. In some cases, the severity symptoms can warrant surgery to help provide enduring relief, and some of these patients do quite well. The treatment gap is composed of patients who either do not want surgery or are poor candidates for surgery due to other health conditions, insurance coverage, or personal reasons. The second bucket is patients who have inadequate response to epidural injections.

Currently, there are no other good treatment options for persistent radicular pain, and we must always consider the risks associated with surgical interventions and postoperative complications, some of which are listed here. Even as delivering anesthesia becomes safer due to improved medications, equipment, and monitoring, there are still risk factors for poor outcomes, and this was found in a large study from Norway of more than 34,000 herniated lumbar disc surgeries. Three percent had a surgical complication; 2 percent had repeat surgery within 90 days; 2 percent had a non-surgical readmission within 90 days; and

7 percent experienced at least one of these unfavorable events. So, while surgery can be a good option for some patients, it still carries risk, and it would be ideal to have an alternative therapy available.

In summary, there are no approved pharmacological therapies for patients with LDH that provide early and long-term reduction in the majority of patients with radicular pain while improving functionality. Alternative treatment options are needed for patients with persistent radicular leg pain who do not respond to conservative therapy and seek non-surgical solutions. That is why I am encouraged by the condoliase clinical results that you will see next.

Thank you. I will turn the presentation to Dr. Stauffer to share those data.

Applicant Presentation - Joe Stauffer

DR. STAUFFER: Thank you, Dr. Wasan, and good morning to everyone here at the committee. I'm Joe Stauffer, Chief Medical Officer to SKK. Today, I will discuss the condoliase clinical

studies that provide substantial evidence of efficacy in appropriately selected patients. I'll start with an overview of the clinical studies and learnings that informed our selection of appropriate patients.

Our primary efficacy data is represented by two positive phase 3 randomized-controlled trials, Study 1031 conducted in Japan and Study 1133 conducted in the U.S. These two studies established substantial evidence of the effectiveness of condoliase. Our pivotal trial in the U.S. study, 1131, did not show separation between treatment and control for the primary endpoint; therefore, SKK initiated a new pivotal study, 1133, based on the learnings from 1131.

To understand the results, SKK conducted an investigation to understand differences between Studies 1031 and 1131 that may have led to the failure. We closely looked across many characteristics of the enrolled population and discovered three key identified differences to patients enrolled in the successful Study 1031 that

were markedly different in Study 1131. These included clear nerve root impingement, lack of chronic low back pain, and lack of opioid use.

Significantly fewer patients in Study 1131 had these factors. The combination of these three factors appeared to explain why 1131 failed to demonstrate a benefit, making it difficult to show a difference between treatment and control. First, a retrospective review of the MRI scans revealed that only 27 percent of people in Study 1131 had confirmed nerve root impingement, but we can't assume that leg pain is due to the herniation because there are other potential causes for leg pain beyond a herniation. This is important because the condoliase mechanism of action is based on shrinking the herniation to diminish the impingement, alleviating the leg pain. That is why MRI confirmation of impingement is important.

Second, the study included many patients with chronic low back pain, but we know that low back pain may confound evaluation of leg pain since it contributes to the overall pain, limiting the

ability to show a difference. And third, over half the patients were using opioids or other concomitant pain medications. This also confounds evaluation of leg pain and can be caused by chronic back pain, also limiting the ability to show a difference.

These learnings from Study 1131 led SKK to work with FDA to design the U.S. pivotal study, 1133. Changes to the inclusion and exclusion criteria were intended to recruit an LDH population that more closely resembled the population from Study 1031, the pivotal phase 3 Japanese study. The key changes were to require confirmed demonstrable nerve root impingement assessed by MRI by both study investigators and the third party central reader. Also, we excluded patients with chronic low back pain of at least one year. We also excluded patients with low back pain from causes other than LDH. And finally, we excluded patients on chronic opioid therapy.

Based on the learnings from Study 1131 and these important modifications, Study 1133 enrolled

a similar patient population to Study 1031. Our interpretation of the data for Study 1131 is limited since the majority of patients had at least one of these key identified confounding factors. With only 25 patients meeting the criteria of our current target patient population, we've limited ability to make any conclusions from the data.

Now, turning to the clinical efficacy results, the remainder of my presentation will focus only on Studies 1031 and 1133 that demonstrate substantial evidence of condoliase efficacy. Despite being conducted in different regions, the demographics in these two pivotal studies were similar. The U.S. study, 1133, had a slightly older population compared to the Japanese study, and both studies had similar numbers of males and females.

Being that Study 1031 was a Japanese study, all enrolled patients were Asian. The majority of patients in Study 1133 were white. Some baseline characteristics varied between studies; however, the enrolled patients are representative of the

target indication populations and their respective countries. It is also important to point out the condoliase and placebo or sham treatment arms are similar when looking at each study individually.

Now, let me take you through the study design. The design of Studies 1031 and 1133 were similar. They enrolled adults ranging from 20 to 70 years of age with LDH at L4/5, or L5-S1, or L5-L6. Patients were randomized 1 to 1 to either condoliase 1.25 units or a placebo sham injection. The primary endpoint was changed from baseline to week 13 in worst leg pain using the 100-millimeter Visual Analog Scale score. All patients were followed for 52 weeks.

Study 1133 remained blinded throughout 52 weeks. For Study 1031, everyone was blinded through week 13. After week 13, the 1031 data was unblinded only to SKK but not the investigators and patients. For both studies, treatment assignment was not shared with investigators and patients until the database was locked at week 52.

Let's look at the endpoints. Efficacy

endpoints were also shared across studies. As I mentioned, the primary endpoint for each study was changed from baseline in average worst leg pain score on a VAS at week 13 using an MMRM analysis. The primary analysis used MMRM without imputation, assuming data were missing at random. Secondary endpoints included change from baseline in average worst leg pain score at week 52, herniation volume at week 13, and Oswestry Disability Index, or ODI, score at week 13. I'll outline each of these methodologies for assessing pain in more detail.

Worst leg pain was assessed using the 100-millimeter Visual Analog Scale score or VAS. Patients indicate their worst pain in the past 24 hours along a horizontal line, which ranges in intensity from no pain to pain as bad as you can imagine. A patient's VAS recording is the distance in millimeters from zero or no pain to the pain intensity they indicated.

Herniation volume was assessed using MRI scans that were sent to a central imaging facility for analysis. Lumbar disc tissue margins were

outlined on each slice. Herniation volume was calculated as the cross-sectional area measured in each slice multiplied by the slice separation. Total herniation volume was therefore equal to the sum of the volume measurements from each slice.

The Oswestry Disability Index is a questionnaire containing 10 items of daily living, which are shown here. Each of the 10 items contain 6 statements to assess a patient's disability. The statements are given a score from 0 to 5, with 0 being no disability and 5 the greatest disability. A total score is then calculated by adding the completed items and dividing by the maximum score, then multiplying by 100 to get a percentage. A higher score indicates a higher level of disability.

Let's look at the results. Condoliase met the primary endpoint in the two pivotal studies, showing a significant improvement in worst leg pain at week 13 compared to the placebo group for Study 1031 on the left and compared to sham for Study 1133 shown on the right. Here, I'm showing

cumulative distribution plots for Studies 1031 and 1133 at week 13. The total percentage of patients is shown on the Y-axis. On the X-axis is the percent reduction in pain from baseline to week 13 such that the line represents the cumulative number of patients that achieve that threshold for pain reduction. For example, 78 percent and 68 percent of patients achieved a 30 percent reduction in pain at 13 weeks in the two studies. In comparison, the sham arm showed that 59 percent and 57 percent attained a 30 percent reduction in pain.

Now, looking at a 50 percent reduction in pain, we see that 72 percent and 62 percent of patients achieved this threshold at 13 weeks in the two studies. In comparison, only 51 percent and 49 percent achieved this threshold with sham. For both thresholds, the effect sizes are similar. Overall, consistently more patients treated with condoliase achieved all levels of pain reduction compared to the placebo group.

Next, I will review the secondary endpoints. Looking at long-term efficacy in Study 1133, we

observed improvement in worst leg pain with condoliase compared to placebo at week 52. This was not a prespecified endpoint in 1031. When looking at change in weekly averages of worst leg pain, we saw consistent and similar results between the studies. Patients treated with condoliase achieved durable improvements in their pain across the full 52 weeks.

Looking at herniation volume across both pivotal studies, there was a numerical improvement in herniation volume at week 13 over placebo. There was also a numerical improvement in ODI score at week 13 over placebo. Both trials involved patients who, on average, had a moderate level of disability according to their ODI. By the end of 13 weeks, patients in both trials improved in their disability from moderate to mild on average. Overall, the efficacy data showed that condoliase consistently provided patients with early and durable benefit.

Let me summarize that totality of the data starting with Study 1031. Regardless of endpoint,

we see a point estimate that consistently favors condoliase, and the prespecified SF-36 quality-of-life assessments support the efficacy endpoints, supporting that the results are meaningful to patients. This consistency is also seen with Study 1133. Here, we see that totality of the data in Study 1133. Again, we see that regardless of point estimate, the point estimate consistently favors condoliase. Again, all quality-of-life assessments support the efficacy endpoints, supporting a meaningful benefit. These results provide confidence in supporting substantial evidence of effectiveness.

We also have supportive evidence from Study 1133 that the proportion that went on to have surgery for their LDH is reduced with condoliase. During the first year following treatment, fewer condoliase patients treated went on to get surgery to correct their pain. While the difference did not reach significance, it is a good leading indicator for longer term benefits beyond one year. Study 1031 did not show a difference at 52 weeks

but did show reduction in surgery when patients are followed for up to 5 years.

Here, we show published post-treatment follow-up data of a median of 2 to 5 years that was collected via a systematic survey and evaluation of reconsented patients who participated in the two randomized-controlled studies conducted in Japan, Studies 1021 and 1031. We again see separation with fewer condoliase patients receiving surgery for LDH at the same target level than the placebo-treated patients. These results align with expectations based on the mechanism of action. The reductions in LDH volume diminished the radicular leg pain and diminished the need for surgery.

Let me conclude the discussion of efficacy by sharing why efficacy results are clinically meaningful. In summary, the clinical data demonstrate that condoliase provides meaningful efficacy and an alternative option for patients who want to avoid surgery or are ineligible for surgery. Patients treated with condoliase received significant pain relief, which was demonstrated in

two pivotal studies that met the primary endpoint.

Condoliase also demonstrated an improvement in both early and durable relief of worst leg pain and reduction in herniation volume compared with the control group. Further, the condoliase group saw an improvement in function in the Oswestry Disability Index that persisted over time. Overall, the clinical study data show that condoliase provides patients with significant and clinically meaningful benefits as an alternative to surgical intervention.

My colleague, Dr. Martire, will now present the safety findings.

Applicant Presentation - Diane Martire

DR. MARTIRE: Thank you. I'm Diane Martire, and I'm a safety advisor to SKK. I'll now review the safety data that demonstrates that condoliase is well tolerated with an acceptable safety profile in patients with LDH.

In agreement with the FDA, the safety database included 1500 patients exposed to condoliase, with 300 followed for at least one year

and 150 followed for at least 2 years. Overall, the ISS included 1679 patients who received condoliase, exceeding the agreed-upon number of required exposures for all durations of follow-up. The primary safety data set included the four phase 2 and 3 randomized-controlled studies. This pooling strategy was agreed upon with the FDA in the type B pre-BLA meeting. The data I'll present today include only patients who were treated with the 1.25-unit dose.

Shown here is a summary of safety at various time points from day 0 to the primary endpoint at week 13 and through week 52. For Studies 1021 and 1031, after week 13, only SAEs and AEs related to the intervertebral disc were recorded. In both groups, most adverse events occurred within the first 13 weeks. Rates of severe AEs and SAEs were low and occurred at similar rates between treatment groups. There were few discontinuations due to adverse events, and no deaths were reported within the first 13 weeks. No deaths were assessed as related to study drug. Overall, no clinically

meaningful safety signals or imbalance in safety reporting have been identified.

Here, we see AEs that occurred up to week 13 in more than 3 percent of patients. Back pain occurred most often in both treatment groups. The most common events in condoliase-treated patients were back pain and MRI spinal abnormal. Back pain is to be expected with injection of the product directly into the disc, and the MRI spinal abnormal AEs are all modic changes, which will be discussed in detail by the next presenter.

Given the FDA's interest in back pain, let's look more closely at these events. Here, we show all back pain adverse events reported throughout the pooled studies by time of onset. In line with expectations for an injected product, we see that the imbalance occurs early, within the first 7 days following injection. After that time, new onset back pain events are balanced. This is also confirmed by looking at back pain AEs after week 13.

Overall, MRI spinal abnormal -- that is,

modic changes -- and back pain were the most common events reported for condoliase from week 13 to week 52. In line with the previous slide, the frequency of back pain AEs, shown in the middle of the table, is greatly reduced compared to the first 13 weeks of follow-up and is now balanced between the treatment groups.

There were a few serious adverse events that occurred up to week 13, and no preferred terms were reported in more than two condoliase-treated patients. When looking after week 13, the only event that occurred in two or more patients at each time point was intervertebral disc protrusion. Rates were very low and didn't occur in placebo/sham group after week 26. When looking at long-term adverse events that occurred after week 52, we saw a similar percentage of AEs between treatment groups. These data include only Study 1131. MRI spinal abnormal modic changes and back pain occurred most often at its similar rates in both treatment groups.

Now, turning to select safety topics of

interest, we identified these select safety topics of interest that warranted additional investigations due to identified or potential risks. Overall, safety topics of interest AEs occurred at a low frequency and narratives for these events have been provided in your briefing document. For this presentation and based on the mechanism of action and proposed labeling, I'll focus on hypersensitivity, anaphylaxis, and spinal abnormalities.

Protein-based drugs are known to carry risk for anaphylaxis and hypersensitivity, so we looked at the narrow standard measure queries for hypersensitivity and anaphylactic reaction. Overall, hypersensitivity events occurred in 4 percent of patients in the condoliase group compared to 3 percent in placebo or sham group. Rash was the most common event, and none of the rash AEs were serious. There were no anaphylactic reaction events reported in the clinical trials.

Moving to spinal abnormality adverse events, there were few spinal abnormalities of interest,

which were adverse events as reported by the investigator. These occurred in 5 patients or approximately 1 percent of patients in both treatment groups across time intervals. Most events occurred more than 13 weeks following injection, with two condoliase patients having an AE of spinal osteoarthritis compared to one in the placebo arm.

To summarize safety, condoliase was well tolerated with an acceptable safety profile for patients with radicular leg pain associated with LDH. Overall, the majority of AEs were mild or moderate in severity, and rates of SAEs were similar among patients who received condoliase versus control. Hypersensitivity was infrequently reported. Most events were mild to moderate in severity. There were no reports of anaphylaxis. Spinal abnormality AEs as reported by the investigators occurred in about 1 percent of patients in each treatment group. SKK also separately investigated imaging findings, which will be discussed at length by the next presenter.

Before turning the presentation over, I'll briefly share what we've seen so far in the postmarketing setting. As of the 4-month safety update, the postmarketing safety database includes an estimated 27,000 patients and is consistent with the safety profile observed in clinical trials, with most events related to pain or hypersensitivity. Highlighted in yellow are the events related specifically to hypersensitivity.

Although infrequently reported, SKK acknowledges that protein-based injected product like condoliase carried the potential for hypersensitivity, including anaphylaxis, and we take this very seriously. There have been three reports of AEs in the anaphylactic reaction SMQ in the postmarketing experience. All these events resolved without sequelae.

Because of these events, language around this topic will be included in the warnings and precautions section of the proposed product label. Post-injection monitoring will align with practices used with epidural steroid injection and will

include monitoring for vital signs, pain, and neurologic status. We also intend to provide a patient leaflet advising patients to seek appropriate treatment should they experience rash or serious hypersensitivity symptoms.

I'll now pass the presentation to Dr. Fuerst to review the imaging findings.

Applicant Presentation - Thomas Fuerst

DR. FUERST: Thank you. I'm Tom Fuerst, and I'm the Chief Science Officer at Clario and a Radiology Consultant to SKK. SKK prospectively conducted imaging to evaluate the potential for incremental long-term disc degradation following a single injection of condoliase. X-ray and MRI imaging was collected over the course of the studies from screening through week 52 and an additional week 104 time point in Study 1131.

Imaging at each time point was assessed by a central reader for prespecified changes suggestive of disc degeneration. These included a decrease in disc height from baseline of at least 30 percent; intervertebral body angle and flexion posture of at

least 5 degrees; and intervertebral body dynamic translation of at least 3 millimeters.

We also evaluated for modic changes in the adjacent vertebral bodies, where modic type 1 represents inflammation in the adjacent bone marrow; modic type 2 represents fat conversion following the inflammation; and modic type 3 indicates bony sclerosis. It's important to note that these imaging findings were reported based solely on the observations made in the X-ray and the MRI images without regard to symptomatology or patient complaint.

Let's look at the results. Analysis of spine X-rays showed more condoliase-treated patients had a decrease in disc height of at least 30 percent from baseline, consistent with the method of action. The other criteria, which the scientific literature associates with spinal instability, were observed infrequently and at similar rates between condoliase and control groups, suggesting that treatment with condoliase does not worsen spinal stability.

While modic changes were observed with similar frequency in both groups at baseline, new modic type 1 change was more frequent in the condoliase group, occurring at a rate of 27 percent of patients at week 13 compared to 5 percent in the placebo/sham group. By week 52, the rate in the condoliase group showed a small increase to 32 percent while the placebo/sham group showed a larger steady increase to 15 percent. In contrast, the incidence of more advanced changes, identified as modic type 2 and 3, was much smaller and similar to placebo or sham.

While there has been no direct comparison between discectomy and condoliase, data from the scientific literature suggest that the imaging changes observed after condoliase treatment are of the same type and similar frequency as changes observed post-surgery. Notably, we also observed disc height loss in the control arms of the clinical trials of 7 percent at week 52.

We investigated the clinical significance of imaging findings after condoliase administration

but found no consistent relationship with leg pain or back pain. Nevertheless, to further understand the potential risks of condoliase treatment, an expert neurosurgeon, Dr. Kee Kim, reviewed the data study patients with imaging findings. He will present the results of his review next.

Applicant Presentation - Kee Kim

DR. KIM: Good morning. I am Kee Kim, a Professor of Neurological Surgery at UC Davis and the Chief of Spinal Neurosurgery and Co-Director at the UC Davis Spine Center. I am pleased to be here today to provide my clinical perspective on condoliase for patients with lumbar disc herniation. As you heard earlier, I was asked to review the imaging changes observed after condoliase administration, and I'd like to begin by sharing the key points of my review.

In my evaluation, I reviewed all patients who exceeded the prespecified thresholds that Dr. Fuerst just discussed. I also reviewed those who had LDH surgery at the treated level. I carefully reviewed all of the patient profiles,

which include demographics, concomitant medications, medical history, and adverse events. I also reviewed results from their neurological exams, function and disability questionnaires, and leg and back pain VAS plots. Overall, my goal was to interpret the clinical significance of the imaging findings and identify any increased risk or relationship to clinical outcomes.

First, it's important to note that disc height loss and new modic changes are known to occur with the natural history of LDH, and we see individual variation regarding association of these changes with patient outcomes. After reviewing the data from the condoliase clinical trials, I concluded that the imaging findings did not have a clear association with clinical outcomes.

I can say that confidently since there were no differences between patients with and without imaging AEs in leg pain scores or ODI through one year follow-up and post-study out to 5 years. Some patients with modic type 1 changes had concurrent back pain in both treatment groups, but the

clinical relevance of these changes is not well established.

These observations were aligned with the mechanism of action of condoliase and the natural course of the disease, and the magnitude was not predictive of functional impairment. Overall, the imaging findings were not clinically meaningful, with no observable impact on pain or functionality at 13 or 52 weeks.

Now, turning to the need, as you've heard from Dr. Wasan, our first line of treatment for patients with radicular leg pain associated with LDH without significant neurological deficit is conservative, and it works for most patients. We can typically try different conservative methods or combinations of therapies to achieve adequate pain relief; however, patients who don't respond to conservative therapy end up having surgery.

While many patients are satisfied with surgery, it still carries risk and the potential for residual pain. Of course, every treatment decision must be in the best clinical interest of

the patient. Some are not candidates for surgery due to age or comorbid conditions. If the risks are too high, in my clinical opinion, I don't recommend surgery for that individual.

For these scenarios, patients are still in desperate need of therapy but currently have no other options. That is where condoliase could fill the treatment gap. Importantly, patients treated with condoliase will still be candidates for surgery later on, even at the same disc level. For many patients enduring leg pain due to LDH, avoiding surgery is an important treatment goal. Some patients don't want surgery or aren't willing to accept the associated risks and recovery, and will continue to suffer with their pain or limit their lifestyle to avoid activity.

I've had patients with insurance issues and other personal situations that make surgery a challenging and sometimes impossible treatment option. Condoliase provides an effective and well-tolerated option for patients to reduce LDH volume that allows them an alternative to surgery,

as demonstrated by long-term follow-up data shown earlier by Dr. Stauffer. Consistent with the mechanism of action, condoliase provides meaningful improvements for patients by shrinking the lumbar disc herniation, removing impingement from the effective nerve root, and relieving the leg pain caused by the nerve root impingement.

Here, you can see images of herniated disc from a condoliase study patient throughout the course of the trial. The yellow arrows point to the clear protrusion of the nucleus pulposus at screening that is quite large. The idea of internal treatment could shrink disc herniation, diminishing the pressure on the nerve root to relieve the patient's pain without needing a discectomy.

We can see that the herniation improves early at 6 weeks after the single condoliase injection and continues through week 52. The pain relief associated with these changes is clinically meaningful to patients. I've had patients tell me that the pain relief provided by condoliase has

restored their usual functioning and gave them back the ability to do everyday tasks they could no longer do, and they were able to achieve this without surgery.

Importantly, confirmation of visible nerve root impingement would allow appropriate patient selection. This makes perfect sense since we should only expect condoliase to improve leg pain when it is linked to a herniation causing nerve compression. If there is no impingement, then reduction in herniation volume will not alleviate the pain.

Fortunately, MRI confirmation of impingement is standard practice and readily apparent on imaging, as shown in the scans. Conversely, when there is no contact whatsoever, there is clear separation between the hernia and the nerve. From my perspective, the benefit-risk assessment is positive, and I hope to have condoliase available as an important additional therapy option for patients. Thank you. I will now turn the presentation back to SKK.

Applicant Presentation - Joe Stauffer

DR. STAUFFER: Thank you, Dr. Kim.

Before we take your questions, I'd like to briefly conclude with the benefit-risk assessment for condoliase. We've heard today that there is a clear unmet need for an effective and safe therapy for radicular leg pain in patients with LDH. In two pivotal studies, condoliase met the prespecified primary endpoint, demonstrating significant and clinically meaningful improvement in both early and durable relief of worst leg pain. It also demonstrated reduction in herniation volume and improvement in function at week 13 that persisted over time. Regarding safety, condoliase was well tolerated with an acceptable safety profile across clinical studies. It has been well characterized through clinical use and postmarketing surveillance in approximately 29,000 patients.

Condoliase gives patients with radicular leg pain due to LDH the option to receive an effective and well-tolerated therapy to diminish leg pain,

and labeling and awareness of the study results, including Study 1131, will reinforce use of condoliase in appropriately selected patients. This begins with reserving condoliase as an option for patients that have had an inadequate response to conservative therapy and requiring radiological confirmation of visible nerve root impingement by the herniation. In fact, clinical situation and learnings help diminish concerns about patient selection or safe administration.

Patients unresponsive to conservative therapy will be treated by trained specialists who are experienced with spine injections. Awareness that patients without impingement are unlikely to benefit will prompt confirmation of nerve impingement. Thank you, and we look forward to your comments.

Clarifying Questions for Applicant

DR. BATEMAN: Thank you.

We will now take clarifying questions for the sponsor. When acknowledged, please remember to state your name for the record before you speak and

direct your questions to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it'd be helpful to acknowledge the end of your questions with a thank you and the end of your follow-up questions with, "That is all for my questions," so we can move on to the next panel member.

Are there any clarifying questions for the presenters? We'll start with Dr. McCann.

DR. McCANN: Thank you. My question first question is for Dr. Martire. Do you have any data about repeat injections from the Japanese population?

DR. STAUFFER: Hold on, Diane. We need to get the microphone up. I apologize.

DR. MARTIRE: Diane Martire, safety.

DR. STAUFFER: There we go.

DR. MARTIRE: There have been anecdotal reports in the postmarketing experience of repeat injection with no untoward effects reported, one case. I have no other information.

DR. McCANN: So there's been one case of repeated injection or there's been one adverse reaction in the --

DR. McCANN: One case of repeat injection in the postmarketing, inadvertent, but it was recorded, and there was no adverse event associated.

DR. McCANN: Okay. So the 29,000 people, there was not a patient that went on to herniate a disc at a different level --

DR. MARTIRE: No.

DR. McCANN: -- that got treated.

DR. MARTIRE: The natural history of the disease, which one of my colleagues can speak to more expertly, there were patients who went on to have surgery because of herniation at a different level.

DR. McCANN: Okay. Alright.

My other question -- thank you -- is for Dr. Stauffer.

DR. STAUFFER: Yes.

DR. McCANN: I guess I'm trying to figure

out what the pool of patients are in the United States that meet the criteria, meaning how difficult was it to recruit the patients who had herniation who were not exposed to opioids and had no low back pain.

DR. STAUFFER: So not exposed to opioids and had low back pain, and still recruited into the trial?

DR. McCANN: Yes, for Study 1133. Is that 10 percent of the population of people with herniation?

DR. STAUFFER: I can speak to there are populations of patients for clinical trials, and then populations of patients for clinical practice. In clinical trials, it's often harder to recruit patients because you have to meet certain inclusion and exclusion criteria. I think, as we pointed out here -- and I have a slide to show you, if it comes up -- we're talking about 1 to 3 percent of the U.S. population with this particular condition. Now, many of these patients, some are on opioids and some are not. Also, some have low back pain as

well. Low back pain is not always caused by lumbar disc herniation and not all lumbar disc herniations necessarily have spinal root impingement either.

So, it was a manageable trial. The second one was more difficult during COVID, but manageable, and we were able to get them. I do think that there is a cohort of patients out there that need this therapy. The mechanism of action lends itself to that. Again, it's only for patients, though, who have failed conservative therapy, so those conservative therapies 6 weeks or longer.

I can have perhaps Dr. Ahmed discuss also the broader population of patients.

DR. McCANN: Sure.

DR. STAUFFER: Because you're asking about what might be out there in the clinical --

DR. McCANN: But I just want to know -- you've mentioned the word "cohort" -- exactly how large this cohort is anticipated to be.

DR. STAUFFER: Dr. Ahmed?

DR. AHMED: Of the patients that have been identified -- Raza Ahmed, Medical Director with Ferring; excuse me. Of the patients that do fit the criteria that Dr. Stauffer just spoke about, we anticipate about 20 to 50 percent of those patients can potentially be candidates, based on the clinical evaluation of the specialists that they've worked with.

DR. McCANN: Thank you.

DR. BATEMAN: I have a question for Dr. Stauffer, and this relates to the negative trial, 1131. Can you show the results with respect to the primary endpoint for the subset of patients with evidence of nerve impingement on MRI?

DR. STAUFFER: So you're looking for a subset analysis --

DR. BATEMAN: For the 69 patients that had imaging-confirmed nerve impingement.

DR. STAUFFER: I understand. Ben Vaughn, who is our statistician, will discuss for you.

MR. VAUGHN: Ben Vaughn, statistics. What we run into there is that we just get into a small

sample size problem. While we do have a number of subjects that do have the clear nerve root impingement, only 21 subjects in the sham group fell into that category, so the results are very unstable. Once we factor in some of these other compounding factors, it's really hard to interpret results from something like that. We get down to just 5 target patients in the sham group and 20 in the active group.

DR. BATEMAN: Are you able to show the results for the 79 versus the 21? I recognize the confidence intervals will be wide and the results unstable, but can we see the the effect size for the primary endpoint?

MR. VAUGHN: Sure. Here, just focusing on the active groups, again, this gets it down to the subjects with chronic low back pain or without the impingement; that's the upper line, and the lower line are the patients that we would consider to be more of our target population and don't have chronic low back pain and do have the clear impingement, so you can see the effect of that and

how they're improved. Thank you.

DR. BATEMAN: Can we see the results for the 69 where you had MRI evidence of impingement? That's not shown here.

MR. VAUGHN: Sure. We do not have that prepared, but we can potentially --

DR. BATEMAN: Maybe after the break.

DR. STAUFFER: Sure.

MR. VAUGHN: Thank you.

DR. BATEMAN: Dr. Stojanovic?

DR. STOJANOVIC: Thank you. We have acute disc protrusion. There are two reasons for having radicular pain. One is the mechanical compression of the nerve root; the other one is chemical inflammation. Where you have complete annular tear, the disc material leaks out. And it's recognized as a foreign body because it's kind of an immunological privilege. That's why we have acute radicular pain from chemical sensitization of nerve root, so there are two reasons you can have radiculopathy.

So there are cases when you don't have

complete annular tear; you have contained disc herniation, so this concept makes sense. I just haven't heard what happens if you have a complete annular tear. You have a leak of the disc material, so if you're applying this treatment, how is the disc going to shrink where the disc material is leaking? This is one question.

The subquestion is what happens if you administer condoliase where you have a complete annular tear, where the medication actually leaks out? Are there any problems with this? I have two other subquestions after this, so this is the first one.

DR. STAUFFER: The first question was about annular tears, the herniation leaking out. I think that was the first piece.

DR. STOJANOVIC: Yes, the first piece, leaking out, how would the disc shrink if the disc has leaked out already? And the other thing is, once you administer the medication, would the medication leak out and cause any problems?

DR. STAUFFER: On the first part of your

question, this biologic is only indicated for those disc herniations that are not leaking, so it's only indicated for those. If I could show a picture here, it might provide a little bit more clarity on the types of protrusions that we have. Again, it's only indicated for those, and I'll have Tom Fuerst discuss the rest of your question.

DR. FUERST: Tom Fuerst, radiology advisor. With regard to selection of patients for the trials, we included both patients that had tears and without tears. We saw response, as you saw it in the total group. We didn't look specifically at those with and without tears, but we do believe by the method of action, we would still have reduction in the size of the herniation, even if there's a tear present.

DR. STOJANOVIC: Well, what the indication for the treatment would be at the absence of complete annular tear.

DR. STAUFFER: I think that would be the appropriate part for the indication. I could have Dr. Fuerst comment.

DR. FUERST: Tom Fuerst. No, I don't think that would be a part of the indication. We studied both herniations with tears and without tears.

DR. STOJANOVIC: One more subquestion for you that's different. You showed a decrease in disc protrusion after treatment. Are there any data to compare the natural course of disease? We know that the disc can shrink with time and with surgery, so surgery, natural versus treatment.

DR. FUERST: Yes. Thank you. In the trial, of course, we had the control arm, and we did see a reduction in herniation size in the control arm as well. The reduction with condoliase treatment was larger than in the control arm. But you're correct; there is a natural resolution of herniation as the disc naturally dehydrates and shrinks.

DR. STOJANOVIC: With surgical data after discectomy.

DR. FUERST: Oh, I'm sorry.

DR. STOJANOVIC: In comparison to after discectomy reduction of disc; is it comparable to

discectomy data? Do we have any studies on that?

DR. FUERST: Yes. I don't have direct information about that. With regard to surgical discectomy, it really is dependent upon how aggressive the surgeon is and how much disc material they remove, and their different schools of thought with regard to that.

DR. STAUFFER: Perhaps Dr. Kim could add some color to that commentary.

DR. KIM: Sure. Kee Kim, neurosurgeon, and Dr. Fuerst actually did a good job. It really depends on how aggressive you are as a surgeon in terms of discectomy. We have moved away from doing really aggressive, where you try to not only remove the offending disc but also remove additional discs, thinking that you're going to reduce the risk of recurrent disc herniation.

So now, a lot of surgeons are just removing the offending disc. So even with that, I suspect that if you actually get the MRI, depending on how much more you remove, as opposed to condoliase treatment, I suspect it will favor surgery in terms

of actually being able to visualize that.

DR. STOJANOVIC: Thank you very much.

My last question is regarding the outcomes. If you look at the forest plot data, figure 32, basically you have mean data and categorical data. Here, we have categorical data, 32, and 50 percent of the patients, they have positive outcome in between treatment and placebo or sham. So the difference is statistically significant but not in all places, and it's not that impressive.

Just looking at the other things that might improve, and narrowing selection criteria, if you look at the forest plot in figure 32, it looks like the patients' disc degenerates with age, so patients who were older actually did not respond as well. The forest plot doesn't favor condoliase treatment if you look at figure 32.

DR. STAUFFER: This is a different look at the forest plot data, and I can have Ben Vaughn comment more on the statistics. But there are other endpoints that matter, not just pain, as part of the overall package for the drug, and certainly

the disability index, as well, is important. So, we believe it's important to remember that these patients do get a pretty nice response. It is statistically significant and clinically relevant in both clinical studies that we had, understanding there are clearly differences in certain of the ages.

Ben?

DR. STOJANOVIC: It's a different slide, figure 32.

DR. STAUFFER: I'll bring it up.

MR. VAUGHN: Perfect. Ben Vaughn, statistics. We do acknowledge that the estimates bounce around a bit, and you will note that there are some very wide error bars on there. We get into some small sample sizes. For example, in 1031, 50 to 59 years old, it's 10 versus 7 subjects.

So inference is a little difficult once you get into that, but you'll notice across the board, in that yellow zone, any time that you see the bold blue dot there in the yellow zone, that favors

active. So, the overall picture of this is we are falling on the appropriate side of that line; and, yes, sometimes the error bars do extend past that and its small sample size.

DR. STOJANOVIC: Thank you. Those are all my questions.

DR. BATEMAN: Okay.

Dr. Sprintz?

DR. SPRINTZ: Hi. Michael Sprintz. This is a question for a Dr. Stauffer. On slide 85, we're going to be voting on -- or at least as it's currently written -- using condoliase for the treatment of radicular pain associated with confirmed nerve root impingement caused by LDH, but you've also talked about the indication. Why does that indication that we're voting on not mention patients who failed conservative therapy but is really only for MRI confirmed, or will that be it?

DR. STAUFFER: We would clearly expect that to be part of the label as well, described in the clinical studies section, so those patients who are failing conservative therapy.

DR. SPRINTZ: Okay. Yes. Great. I just wanted to make sure that was a part of that.

DR. STAUFFER: Thank you.

DR. SPRINTZ: And then for Dr. Martire, you said that you intend to distribute a patient leaflet about hypersensitivity reactions. I mean, we know the patients rarely will read the product information label when they're getting the procedure done. So my question is, is it an intention to do that or is this something that the company will do?

DR. MARTIRE: I'll refer this to Dr. Ahmed.

DR. STAUFFER: We'll take it to Dr. Ahmed.

DR. SPRINTZ: Oh, okay. I apologize.

DR. STAUFFER: That's okay.

DR. AHMED: Raza Ahmed, and I'm with Ferring. We do plan on distributing a patient leaflet post-injection, so we will do that.

DR. SPRINTZ: Okay. Thank you.

DR. BATEMAN: Dr. McAuliffe.

DR. McAULIFFE: Hi. This is for Dr. Stauffer as well. I heard you say several

times that the patients were having noticeable and meaningful efficacy --

DR. STAUFFER: Right.

DR. McAULIFFE: -- and I was looking at the data at Study 1133 and 1031, which were your positive primary efficacy studies. And on the visual analog scales, it's at week 13 minus 7.5 and minus about 15 millimeters. And I'd like to see that in context a little bit more. Is that really a robust noticeable difference in pain, and are there any studies that compare that to more conservative therapies, visual analog scales and surgical scales?

DR. STAUFFER: For chronic pain trials, whether they're oral medications, topical medications, et cetera, in low back pain as an example, or even in this case in radiculopathy, about a 10-point change on a 100-point scale is clinically meaningful. There are other elements I can discuss as well, but in this case, it's, on average, about a 0.4 effect size, which is pretty robust, believe it or not.

That was Study 1031; that's the effect size down to 0.26 for Study 1133, with an average effect size of around 0.3. That is a modest effect size and meaningful effect size just in pain alone. When you add that into the other elements as part of a patient's experience, not just their pain score but also their disability, what that does, and also the relatively benign safety profile, that's clinically meaningful to patients.

I can just bring up this slide just to give you an example of what opioids might look like. These are effect sizes for opioids. What we have here is a therapy that's non-opioid and non-NSAID, and you can see that these mean differences are kind of all over the place with oral medications. This targeted treatment with condoliase actually sometimes can outperform those drugs. We're not suggesting that this is better than them, but I'm just trying to provide context for you about is that pain score meaningful, and it is.

I'll have Ben Vaughn also speak to part of the statistics.

MR. VAUGHN: Sure. If we can bring up the core slide with the CDF plots, one other way to look at this is just thinking about 30 percent and 50 percent reduction in pain that's widely accepted to be clinically meaningful, and you can see the gaps between those two lines are the difference in percentage. At 50 percent, we had 62 percent versus 49 percent in the U.S. and 72 percent versus 51 percent. So that's a pretty wide gap in this; 50 percent reduction in pain, which is a very robust clinically meaningful result on an individual patient basis.

DR. McAULIFFE: So is that saying that 49 percent of the patients who had placebo had that 50 percent reduction as well?

MR. VAUGHN: Correct, versus 62 percent inactive.

DR. McAULIFFE: Thank you.

DR. BATEMAN: Dr. Bicket?

DR. BICKET: Thank you. I had a question for a slide that Dr. Fuerst -- CO-74 -- had presented. I know at the bottom, it mentioned

about having no consistent relationship between modic changes in leg and back pain. I was hoping to hear some clarification.

In reading the packet from SKK, later on in the packet -- I think it was around page 97 -- there was some description about an expert reviewer that was interpreting modic changes. I think the sentence had read something on lines of the expert reviewer did note that patients with new modic type 1 tended to be more likely to report back pain. So I was just wondering if you could help clarify those two statements there.

DR. FUERST: Yes. Thank you. Tom Fuerst. If we could have slide DI-16. Nope, that's not the one. It's the modic and back pain slide.

Let me speak to it while this slide is coming up. We saw from Dr. Martire, with respect to back pain findings, a lot of that was focused on the first 7 days after treatment, and we believe it's procedural related. Later in time, we saw those back pain findings were similar between the placebo and control groups, and I wanted to explore

that a little bit more on this particular slide.

Again, looking at the second line here, onset less than 7 days, we see roughly balanced treatment response, or balanced rate of back pain AEs in patients with and without modic changes in both the condoliase group, as well as the control group. The last line here I think is what's most instructive. After 7 days and after the procedural pain has been relieved, we see that patients that have modic type 1 changes in the condoliase group do have a somewhat higher rate of back pain AEs, 15 percent versus 19 percent. But if we look also at the placebo and sham group, we see that we have a similar rate of events and a similar pattern of relationship between presence of modic type 1 change and not. When we looked at leg pain, there was no association or relationship between any of the imaging findings and the leg pain response that patients had.

DR. STAUFFER: If we could have Dr. Kim, as well, comment.

DR. BICKET: I just have one --

DR. STAUFFER: Sorry.

DR. BICKET: -- question while you're still there. Would you just remind us about the follow-up time for the data presented on DI-26?

DR. FUERST: So, this is all the events after day 7. For the two primary studies, that was 52 weeks.

DR. BICKET: Fifty-two weeks. Thank you.

DR. FUERST: Correct.

DR. KIM: Kee Kim, neurosurgeon. I am that expert neurosurgeon that commented on that. I did see, which is not surprising due to mechanism of action, that there was higher incidence of patients with modic change afterwards; and I also found that there was back pain that was reported. But as Dr. Fuerst has mentioned, this back pain tends to be short-lived. And I didn't find a disturbing pattern, which I was looking for very closely when I did this review; could these patients end up with chronic back pain that may lead to a more serious problem later on in life? And I did not find that. In some of the patients that I looked at were out

to 10 years, so I thought I had an adequate amount of info to make that conclusion.

DR. BICKET: Thank you.

DR. BATEMAN: Dr. Kirkpatrick?

DR. KIRKPATRICK: Thank you. I just want to comment that this presentation was excellent, and it represents a huge amount of work. And I know we all know that --

DR. STAUFFER: I thank you.

DR. KIRKPATRICK: -- but I just think it's important to have everybody aware of it. I wonder if you had specific measures of what you're calling clinically significant differences and reference those. That would be my first question.

DR. STAUFFER: The IMPAC [ph] working group -- again, back to pain as an example, what's clinically meaningful to a patient or clinically significant -- on a 100-point scale, about a 10-point movement, and there's data out there to support that. The IMPAC working group, that's actually a collaboration between industry and the FDA, has cited that as clinically meaningful. A

30 to 50 percent reduction is also considered clinically meaningful as well.

So there's clinical significance and clinically meaningful, and they're both the same type of thing; on a 10-point scale, about 1-point movement. On a 10-point scale, if you don't think about VAS is 0 to 100, sometimes people think about it on 10 points. Even a 1-point movement on a 10-point scale is clinically meaningful.

DR. KIRKPATRICK: Additionally for the ODI as a secondary, what did you see --

DR. STAUFFER: Similar, in ODI, on a 100-point scale, 10 to 15 points is actually considered clinically meaningful. I think we actually have some data on 20 percent with our ODI that I can bring up and show you. Let me just show you this score real quick since you're asking about ODI.

Here's our 20 percent improvement. My apologies if it's not coming up. Here it is. This is an important piece that we measured as a secondary endpoint. It's important that these

patients not only get pain relief, which they do, but somehow they can improve their function as well, and this is why we looked at this 20-point improvement. You can see the difference between active and placebo. So again, putting that all together, it's meaningful for patients to be clinically meaningful.

DR. KIRKPATRICK: Thank you. And can you specifically help me understand your sham?

DR. STAUFFER: The sham. That was three different studies. The first study in Japan was placebo injected right into the disc saline. Sham is needle placed exactly the way you would do it if you were going to do a placebo injection into the disc, but the tip of the needle goes right to the annulus but does not penetrate the annulus. So to a patient, they don't know if they're getting an active treatment or a placebo treatment, but it's all done under fluoroscopy the exact same way.

DR. KIRKPATRICK: Thank you.

I am a surgeon, so I am totally immune knowledge void; however, as an orthopedic surgeon,

we often come up with patients with metal allergies, which are challenged. And then their blood is taken, and their blood is challenged, and we get a report as to if there's a response or not. Has that kind of study been considered for condoliase?

DR. STAUFFER: I'm not aware that we've actually studied with metal allergy. Perhaps I could ask --

DR. KIRKPATRICK: I'm not saying it's a mental allergy. I'm just saying that concept.

DR. STAUFFER: So the --

DR. KIRKPATRICK: Does the second challenge induce an immune response?

DR. STAUFFER: I'm an anesthesiologist as well, so I may not have it all like you, but I'll give it to Dr. Martire to answer that question.

DR. MARTIRE: Diane Martire. I'm an internist, so I can make a little bit of an attack on that. We did studies early in the clinical trials looking at antidrug antibody levels, and there was no correlation with the occurrence of

hypersensitivity events. So the antibodies bounced around. We looked at collective IgM, IgA, all of them. We have not done a study measuring specifically antibodies in the postmarketing.

DR. KIRKPATRICK: Thank you.

There's a central reader, and then there was a follow-up with positive responses. Were those readers blinded?

DR. STAUFFER: I will have Dr. Fuerst address your question.

DR. FUERST: Tom Fuerst, radiology advisor. Yes, the central readers were blinded to all aspects of the patient condition, including the site of their symptoms.

DR. KIRKPATRICK: Thank you.

Then, I think this is my final question, and it follows up with what Milan asked. Your document, page 46/figure 18 seems, to be in conflict with something I heard, so I'd like to pull that up if possible.

DR. STAUFFER: Okay.

DR. KIRKPATRICK: And this centers around if

we inject the condoliase in the center of the disc, how does it get to or affect that that's already herniated out? With a secondary question, I heard that if the annulus was disrupted, that was not an indication, so I'm getting confusing things. And you see on your figure, that annulus in the upper left is clearly penetrated by the nucleus. It's not contained anymore.

DR. STAUFFER: Dr. Fuerst?

DR. FUERST: Yes. Tom Fuerst, radiology advisor. Sorry for any confusion. So again, the selection of patients for treatment in the clinical trials included those with and without fissure. The injection of the condoliase into the disc does distribute within the nucleus and would be imbibed by the herniation. We did exclude, however, herniations that were sequestered or free fragments because there would be no communication or connection necessarily with those free fragments.

DR. KIRKPATRICK: And just out of curiosity, when you had patients that had condoliase and went on to surgery, were you able to get the specimens

from surgery to determine whether the herniated disc indeed had normal proteoglycans or had condoliase present?

DR. FUERST: There were no specimens collected in the context of the clinical trials.

DR. BATEMAN: Dr. Jowza?

DR. JOWZA: Thank you. Maryam Jowza from University of North Carolina. I have a question for Dr. Fuerst; actually, it's stacked kind of questions. When we're talking about the modic changes that you found, are these at adjacent levels or is it anywhere in the lumbar spine?

DR. FUERST: Yes. Tom Fuerst, radiology advisor. We only looked at the vertebral bodies adjacent to the treated level. We didn't look at the next vertebral bodies.

DR. JOWZA: Then, can you comment on presence or absence of modic changes in the patients who received the placebo treatment and sham? Were there changes where -- I guess what I'm really asking is, any findings in the patients who actually had a needle inserted into the disc and

received whatever, non- --

DR. FUERST: Saline.

DR. JOWZA: -- saline, yes.

DR. FUERST: Yes. The volume injected was 1 mL, but it is correct, in the placebo group, where there was an actual penetration of the disc and injection of volume, we did see a slightly higher frequency of modic changes in the Japanese group compared to the sham group, but there was no penetration of the disc and no injection of the volume into the disc.

DR. JOWZA: But still less than in the active treatment.

DR. FUERST: That's correct, still less than the active treatment.

DR. JOWZA: And then my final question is, can you comment on types of herniations that possibly the patients responded more central, paracentral, neuroforaminal location-wise? Did you specify or did you look at that?

DR. FUERST: Yes. We were looking at posterior lateral herniations that were paracentral

essentially. Extraforaminal herniations were excluded. And again, we were looking for that impingement of the nerve root, so they necessarily had to be near or in the frame in our central area.

DR. JOWZA: Then, did you exclude patients who specifically also had neuroforaminal stenosis, like the bony stenosis at that same level?

DR. FUERST: That's correct.

DR. JOWZA: You did.

DR. FUERST: The impingement of the nerve root needed to be only due to the lumbar disc herniation. Any bony stenosis or impingement of the nerve root was excluded because those patients may not respond to treatment.

DR. JOWZA: Thank you. That's all.

DR. BATEMAN: Dr. Schiff?

DR. SCHIFF: Yes. Thank you. If I could ask us to take another look at that figure 32 that Dr. Stojanovic had asked us about in terms of the age stratification on the forest plots, in the Japanese study, you had a younger age group, you had a predominant difference of heavy laborers

compared to the U.S. study, and you had people with a lower BMI. If I look at the most significant age stratification, it indeed looks like you might need to restrict to people between 30 and 40 years of age. That seems important.

DR. STAUFFER: I'm going to have Ben Vaughn speak to your question.

MR. VAUGHN: Ben Vaughn, statistics. First of all, a point of clarification, it's not really stratification; this is just the sample that we got with our inclusion/exclusion criteria. And yes, there are fewer subjects in these upper age ranges, which reflect just the demographics of the condition. I think we do have the distribution on the ages overall, but, in general, I'll let Dr. Stauffer speak to this.

In general, you will have subjects in that tighter age range with fewer subjects in the extremes over 60 to 65, but it's potentially a small sample size, random noise, and it's difficult to interpret whether the variability that we're seeing across these age ranges is a true difference

or it's just noise from the sample that we got.

Joe, can you speak to the demographics of the age?

DR. STAUFFER: Sure.

As you can see by the point estimates, there's clearly a distribution there between ages. We see that in both the Japanese study and the U.S. study as well. It's important to recognize these are patients who are failing therapy. They've failed a number of treatments, a number of oral medications. This drug can work for some patients even within this age distribution; however, our best response is, in that age range, I think you had mentioned the 30 to 50 category, that's where we're getting the best response.

DR. SCHIFF: The other question is for both your radiology and your neurosurgical expertise. We've had several questions raised about the integrity of the annulus. If I wanted to test whether my material is going to be retained within the disc or not, I could use a radiological marker under fluoro and ask if it leaks out. It's not

even, I think, as much a tear in the annulus as will your material immediately come into contact with extra disc structures -- the root, facets, et cetera -- and distribute these biological effects well beyond your intended target.

DR. STAUFFER: I'll have Dr. Fuerst answer your question.

DR. FUERST: Yes. Tom Fuerst. It's correct. One could inject contrast into the disc to understand the integrity of the annulus and the potential distribution of condoliase. We don't have experience about that with condoliase. I know, speaking about another agent that performed chemonucleolysis, the chymopapain, that was a technique that was often used, but the extrusion of dye outside of the disc was not a contraindication for the use of that drug, and we don't believe that's a contraindication for the use of condoliase as well because the off-tissue target effects are quite limited, and we have nonclinical data that supports them.

DR. STAUFFER: Just one more commentary,

Doctor, if you wouldn't mind. Our preclinical scientists as well can discuss with you some of the elements that you asked about.

Dr. Spehalski?

DR. SPEHALSKI: Yes. Hi. I'm Liz Spehalski, nonclinical advisor to SKK. The best data that we have is some nonclinical data where we looked at local irritation studies in animals. We did inject condoliase into the intervertebral disc, as well as other spaces, where we looked at local irritation by histology. In all of those studies, we looked at subarachnoidal space, intramuscular, et cetera, and we didn't actually see any irritation, local irritation, by histology in any of the tissues surrounding the disc, with the exception of slight muscle irritation. So we do believe that if there were to be condoliase leaked out of the disc, that there would not be an adverse effect for the patients.

DR. SCHIFF: I looked at your data. The animal data that you injected into had normal discs.

DR. SPEHALSKI: Yes.

DR. STAUFFER: Correct.

DR. SCHIFF: I'd love to hear from your neurosurgeon regarding his thoughts also on injecting an agent to see if your drug is going to be retained in that intervertebral disc space.

DR. STAUFFER: Thank you.

Dr. Kim?

DR. KIM: Yes. I'm a neurosurgeon, so I don't do intradiscal injection. I think that comes into play when we do a discogram and is usually done by interventional radiologists. So maybe --

DR. STAUFFER: Dr. Wasan.

DR. KIM: -- Dr. Wasan may want to speak to that. But from my perspective, this trial was conducted with material injected into the center of the nucleus pulposus, and it is somewhat of a distance away. I do see the concern regarding untoward effect if that leaks out into the subarachnoid space or extradural space; and based on the preclinical data, I do not feel that's something, at least as a clinician, that I'm

concerned about.

Also, a follow-up question that I was wondering is whether that's going to lead to difficulty with surgery, patients who had been treated, and I have a lot of experience with patients who had discogram. So if it's similar to that, I would not expect any difficulty with surgical intervention if those patients are refractory to condoliase treatment.

DR. SCHIFF: Thank you very much.

A final question is, I'm concerned about the decision to go from the placebo control to the sham control trial. You went from what I think was a very powerful design, where the only difference in variable was the presence or absence of the drug. You then went to a design which is confusing in the documents. One says you injected into muscle. You've described it today as injecting close to the annulus itself, but in either case, the placebo trial involved puncturing the annulus. It also involved a 1 centimeter, or 1 cubic millimeter -- not millimeter; it's been a long

day --

(Laughter.)

DR. STAUFFER: Milliliter.

DR. SCHIFF: -- a 1 milliliter injection into a disc that's protruding and causing a pain syndrome.

In the comparison of your placebo and sham results, you've got a 3 to 4 times difference in the placebo injections, causing both leg pain and back pain compared to the sham controls. And if you look at the difference, there's a huge placebo effect here -- I'm using that term twice -- but if you look at the comparison bar plots of the primary result in pain improvement, I think it's 8 points out of 100 --

DR. STAUFFER: That's correct.

DR. SCHIFF: -- difference in pain reduction in the sham versus drug injected in the second U.S. trial.

I'm concerned that you didn't control for the single variable of your drug, and that the maneuver to go to sham enabled you to avoid the

additional pain, which you've also documented from puncturing the annulus, and from that increased volume -- which we have an unfortunate experience neurosurgically in seeing things such as minor trauma to nerves at surgical procedures change pain syndromes, and most of that experience is with the trigeminal nerve. But I am concerned that the increase in volume may have actually had a beneficial effect by causing additional impingement early on. So I'd love to hear some thoughts about that in the U.S. trials.

DR. STAUFFER: So back to why did we go from a placebo injection in the Japanese trial to a sham injection, there's actually a discussion with the FDA and a recommendation from the FDA, from a clinical trials perspective, that even when you inject drug, or anything, even saline, into a disc, that can be disrupted in and of itself. There's certainly infection and other local irritations you can cause there. So what we really wanted to do was to understand, if a patient thinks that they're getting a treatment with this drug, either sham or

placebo, will they get an effect? So that's why the decision was made to go from placebo to sham. In terms of the pain response that patients get, the reality is that this drug will be injected into the nucleus, and to shrink the nucleus, the mechanism of action is there.

So when you look at those two trials, the Japanese and the American trial together, you get about the same kind of ultimate placebo response. There's a huge expectation bias in a trial like this. You can imagine, these are patients who have already suffered through NSAIDs, opioids, et cetera, physical therapy, weight loss. They're not doing well. They're not responsive or they're failing. So we have an opportunity here for an offering for these kinds of patients.

As Ben Vaughn described, we have a pretty impressive treatment effect with these patients at 30 and 50 percent cuts, whether they got a placebo or whether they got the sham. So from what we can see and what we think, there's a benefit there to these patients with reducing the amount of risk

during a clinical trial, and that's, again, back to why the decision was made.

DR. SCHIFF: Thank you.

DR. BATEMAN: I have a question for Dr. Stauffer. So, the proposed indication includes evidence of nerve impingement and one of the key ways in which the second U.S. trial was different from the first --

DR. STAUFFER: Correct.

DR. BATEMAN: -- which was a negative trial. But there were two other really important inclusion criteria that were different between the second U.S. trial and the first, chronic low back pain of greater than a year and excluding patients on chronic opioids.

So I'm wondering if there's been thought of including those other two inclusion criteria as part of the indication. In other words, it would require both evidence of nerve impingement but also be not indicated for patients with prolonged chronic back pain or on chronic opioids to align the indication with the trial that showed benefit.

DR. STAUFFER: I'll come back to your question. Dr. Kim wants to make a comment, but I'll make sure I come back to answer your specific question.

DR. KIM: Kee Kim, neurosurgeon. I wonder if I can provide a clinical perspective because I see these patients all the time in my clinic. A lot of these patients have history of chronic lower back pain, sometimes years, but what's really bothering them is this disabling leg pain. They say, "I just can't live like this. Can you do something?" So if we exclude those patients who had chronic lower back pain over a year, I feel we're taking away potential treatment that would be very beneficial to these patients.

DR. STAUFFER: I can say in your briefing document -- I think this is what you're commenting on, I think page 25 or 26 in table 5 or 4, I believe -- bear in mind that even those patients who had chronic low back pain greater than a year for the failed study, those patients who were on opioid therapy, they do get a treatment effect.

It's just blunted by the concomitant use of other medications.

So to say that patients may not be appropriate, we would acknowledge the MRI impingement for sure must be part of the indication; however, I can bring this up here, patients that I'm bringing up on the screen here, and you can still get a treatment effect that is important for these patients. So whether they had chronicle back pain, or whether they were on opioids or other conditions, again, that effect is blunted from the leg pain primary effect; nevertheless, they do get a treatment effect. It just wasn't as improved as those patients that didn't have that.

DR. BATEMAN: It might be helpful, in addition to providing the data from 1131 with or without MRI impingement, to also see data in the other two subgroups, with prolonged back pain and who are on chronic opioids as well.

DR. STAUFFER: I'll have Ben Vaughn speak to that exact point that you're bringing up here.

MR. VAUGHN: So again, we get into the small sample size problem there, and in particular -- Ben Vaughn, statistics -- the issue is that once we subgroup on the people that do have impingement, we get down to that 27 percent of the subjects. It would be hard to interpret the univariate effect of the chronic low back pain when you're including people that don't have the impingement, so it's a smaller and smaller cut.

Again, just pulling this up so you can see those numbers, the last line is the cumulative. What we get down to is that 20 and 5 subjects, but you could approximate that by multiplying that 28 percent times the subjects with no opioid use, so we might be down around, again, 20 to 30 subjects in each of those subgroups, so it would be hard to interpret.

DR. BATEMAN: Dr. Schiff, you had a follow-up?

DR. SCHIFF: Yes, on your question. The U.S. trial required leg pain greater than back pain, and I really appreciated that straight leg

raising was an important inclusion criteria here. That and the radiological findings all fit with the biological action of the drug. If this is approved for low back pain in a broader spectrum of individuals, it's not at all clear to me that you're addressing what this drug does biologically.

DR. STAUFFER: I'll comment on your comment and question. This drug is only indicated for leg pain, not for back pain. We recognize and understand these two things go hand to hand, but it is clearly only indicated for leg pain, and it'll be specified that way in the label.

DR. SCHIFF: Thank you.

DR. BATEMAN: We're going to take about five more minutes for questions, and then we'll have a break. So we're going to go to Mr. O'Brien next.

MR. O'BRIEN: Thank you. Joe O'Brien, National Scoliosis Foundation. My primary question was just asked by Dr. Bateman. It was rather clear to me, when I was looking at the SKK packet that was sent out, that when you looked at the comparison between the negative study and the

positive study in the United States, on slides 30 and 33, you identified what those components were, the primary components that were considered; yet, when you look at that exclusion criteria, that had changed. It was 4 pages versus 1 and a half pages. I had the same basic question; how is that going to be reflected in the labeling, in particular the chronic back pain and no opioid use?

I did have a question regarding that in terms of it was also concomitant. In the United States, we see many patients that, primarily, if they have any type of nerve pain, they give them gabapentin. I didn't see any reference to gabapentin throughout all of the documentation, and I was curious. Just to have some clarification, was gabapentin the primary use for these patients, both in Japan and the United States? That's one question that I had. The other question, which I'll ask next, has to do with clinical significance.

DR. STAUFFER: Okay. We do have a list of the drugs of patients -- I think if I had the list

of all the concomitant medications; please, we have that as a backup slide. And there's a lot in your question there, so I want to make sure I get to your points.

If I could see the list of concomitant medications used. I think this one --

MR. O'BRIEN: As you're looking at that, I was glad to see the data that you did show in terms of the reduction of what the level of surgery was in Japan with the 27[000], or 29,000, depending on what number you're using. I think that real-world evidence is very important. So, as I said, the other case to me in mind is how many people were actually able to reduce off opioids or gabapentin, which is a significant issue with our patient population.

DR. STAUFFER: Okay. You do see it in front of you there, so that gives you a sense of the drugs. I don't have gabapentin specifically. I would imagine it would be here in the antiepileptics part.

Regarding your question on clinical

significance, sir, I'd ask you to give me a moment, so I can make sure I address it correctly.

MR. O'BRIEN: Yes. My basic question is, I assume the patients were looking at a VAS. They were just looking at the smiley faces or the sad faces.

DR. STAUFFER: Yes.

MR. O'BRIEN: If I understand the data, basically at baseline, the patients were at 7.5 on the scale, and the reduction that we saw at 13 weeks was 7.5. Do I understand it correctly? So they're going basically from an 8 to a 7 or a 7 to a 6 on the VAS scale?

DR. STAUFFER: No. On the parametric analysis, all these patients start in moderate to severe pain. That's true in both the Japanese trial and the American trial, around 7, or 70 on a 100-point VAS scale. Over a period of 3 weeks, 4 weeks, 6 weeks, 13 weeks, these patients are moving from moderate to severe pain, which is what you would consider a 7. They're moving down to about a 3 or so.

I think I can show you here. This might give you some more color clarity to answer your question. As you can see, in both trials, you have significant improvement in pain, a pretty robust reduction in pain in the first couple weeks. It stays that way in both trials. It's on the active arm. Of course, the placebo arm is there, but what the patients are feeling is what is going to happen in the real world in clinical practice.

So moving from moderate to severe pain down to mild pain, that's quite significant for these patients. That's quite meaningful for these patients, given the fact that they've tried many other drugs, potentially other therapies, epidural steroid injections, et cetera. So that makes this clinically meaningful just from the pain perspective.

MR. O'BRIEN: Okay. No other questions.

DR. BATEMAN: Thank you.

I'm going to go to Dr. Kennedy. It's the last question, and then we'll have a break.

DR. KENNEDY: Thank you. A couple of

comments and a question; well, one comment. I do really commend this group for doing these studies. This is a lot of work and really hard to do, and it's well done.

Going back to the last slide that was just shown, there were pretty wildly overlapping confidence intervals in that. I completely agree with the notion of 30 or 50 percent pain reduction being very significant among patients. The 10-point reduction or 1 point on a 1 to 10 scale is pretty debated in the literature, meaning there are a lot of studies showing that you need significantly more than that to even hit a minimal clinical important difference. In my experience, most of my patients going from a 6 to a 5 do not feel that different.

My question, though, is really directed at the best results do appear in the younger group, which makes sense given the natural history of the disease, and we know that a 20 year old has a very different back than a 70 year old, both in natural history and future costs, et cetera. Given there

are studies showing a larger decrement in disc size, firm, and grade, et cetera in younger people, and this by definition is the start of the degenerative cascade in the spine where you start with a disc degeneration followed by facet arthrosis, stenosis, et cetera.

What is a time frame we would be looking at to really assess that -- because it's probably not something you would see early -- given the specifically more robust results in the younger group? Thank you.

DR. STAUFFER: Thank you. I'm going to have Dr. Fuerst address your question.

DR. FUERST: Yes. Tom Fuerst, radiology advisor. With regard to the disc height loss itself in younger versus older, we really didn't see any difference in terms of the magnitude of disc height loss over time between the younger and older individuals, and over the course of time, any consequence of that loss of disc height may take some time to manifest.

We do have information in the Japanese

patient population in the survey study that was mentioned by Dr. Stauffer out to 5 years, and over that time, we did not see any further loss of disc height between 1 year and 5 years, and we didn't see any change in the pattern of imaging findings, and there were still pain benefits out that long.

DR. STAUFFER: Again, Dr. Kim for the surgical commentary.

DR. KIM: Kee Kim, neurosurgeon. Yes, I want to provide the clinical perspective. Patients, even with the disc height loss, if they're symptomatic, obviously, we want to note whether that is playing a role in addition to other factors that could be causing their pain, but the reality is that most patients who come to my clinic already have degenerative changes in their spine with modic changes quite often.

Some of these patients, their pain is totally unrelated to radiographic findings. There are many patients that some studies have done, and as we get older, of course, there's degenerate changes that takes place in our body, including the

spine. You would expect disc height loss and modic changes but, thankfully, most of these people are asymptomatic. So what I really want to know is, is there clinical significance, clinical consequence, to these changes, and my conclusion, looking at the imagings, and demographics, and others, I did not see any association in terms of clinical significance.

DR. KENNEDY: Thank you.

DR. BATEMAN: Okay. There are a few outstanding questions, but we'll do those after the FDA presentation, if we have time.

We'll now take a quick 10-minute break. Panel members, please remember, there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 11:15.

(Whereupon, at 11:02 a.m., a recess was taken, and meeting resumed at 11:15 a.m.)

DR. BATEMAN: We'll get started again.

We will now proceed with the FDA's presentations, starting with Dr. Sudhakaran.

FDA Presentation - Shaan Sudhakaran

DR. SUDHAKARAN: Good morning, everybody. My name is Shaan Sudhakaran, and I'm a medical officer with the Division of Anesthesiology, Addiction Medicine, and Pain Medicine. The applicant has kindly presented the clinical trial data. My presentation consists of four topics.

I will start by discussing the clinical condition, mechanism of action, and the intricacies of the disc access procedure. I will cover efficacy next, focusing on how we interrogated and assessed the negative study. In the safety section, I will give an overview of safety, but we'll spend most of the time discussing the adverse events of special interest. Last, I will summarize and integrate our review to this point.

I will now discuss the basic anatomy of a lumbar disc herniation. On the left is an illustration of the lumbar spine. Between the vertebral bodies are the intervertebral discs, which can bulge posteriorly towards the neural structures. On the bottom-right illustration, you

can see an axial view of the intervertebral disc with the gel-like nucleus pulposus in the center, surrounded by the tougher annulus fibrosus. That nucleus pulposus can herniate posteriorly towards the nerve root and cause pain radiating from the lower back into the leg.

The nucleus pulposus is a site of collagen synthesis that contains proteoglycans that facilitate physiologic water retention that result in hydrostatic pressure to resist axial compression of the lumbar spine. The nucleus pulposus can herniate through a damaged annulus fibrosus and compress a nerve root. This can cause irritation and inflammation, and lead to pain, weakness, numbness, and paresthesia in the distribution of the affected nerve root.

Condoliase is a chondroitin sulfate degrading enzyme, which is the predominant glycosaminoglycan in the nucleus pulposus. This can result in reduced intradiscal pressure and volume, and therefore reduced nerve root compression and irritation. On the right is a

figure with the four common types of disc herniation. Panel A is a normal disc; panel B is a protrusion; panel C is an example of an extruded disc where the nucleus pulposus has material outside of the annulus fibrosus; and panel D is a sequestration, where there is pulposus material outside of the annulus fibrosus that is not connected to the main herniation tissue.

Now, I will further discuss the procedure of accessing the disc. The figure on the left is an example of common patient positioning for an intradiscal injection. The patient is positioned prone with a pillow under the abdomen to reduce fluorosis. Under sterile conditions, a fluoroscopy or a C-arm will be rolled in for image guidance. The needle trajectory is from the posterior lateral approach.

On the right, you'll see a series of three images detailing intradiscal access for discography. The needle is initially advanced in the oblique view. We can then see in panel A, the needle is further advanced towards the nucleus

pulposus in the lateral view. In panel B, contrast is administered, highlighting the nucleus pulposus in the lateral view. Needle position and contrast spread is also confirmed in the annular posterior or AP view, as seen in panel C, thus confirming needle placement into the nucleus pulposus in two views.

There are multiple critical anatomic structures in the vicinity of the needle trajectory for disc access. This procedure can be associated with serious risks, including discitis, durotomy, nerve injury, and vascular injury. These complications are rare when performed by an experienced physician who is well versed in the disc access procedure.

Disc access requires detailed anatomic knowledge, fluoroscopic expertise, and meticulous aseptic technique. There can be significant variation with choice of technique, imaging, and periprocedural medications for disc access procedures. While some spine surgeons may perform intradiscal injections, a significant number of

condoliase administrations would likely be performed by interventional pain management physicians or IPM. IPM has a wide array of practice patterns with many specialties and backgrounds actively performing interventional spine procedures.

I will now discuss the efficacy data. The applicant has completed three phase 3 studies, two positive studies with Study 1031 in Japan and Study 1133 in the U.S. Study 1131 in the U.S. was negative. These studies were conducted and analyzed in chronological order, Study 1031, 1131, and then 1133. The applicant reviewed the results from Study 1131 and made multiple modifications to the key selection criteria for Study 1133. We interrogated the data for all three studies with the intent of determining the reason for failure of Study 1131.

This is a high-level summary of the primary efficacy endpoint for the three studies listed chronologically from left to right. The primary efficacy endpoint across the three studies was the

change in worst leg pain from baseline to week 13 after investigational drug administration as assessed by a 100-millimeter visual analog scale. The treatment effect size was the largest for the Japanese study, followed by a more modest effect size for Study 1133. As you can see, Study 1131 failed to meet its primary efficacy endpoint.

Briefly, the patients studied in the U.S. were mostly Caucasian, middle-aged patients with a significant rate of baseline medical conditions. Patients in the Japanese phase 3 study, or Study 1031, were younger, had a lower BMI, and a higher proportion of patients working in heavy labor when compared to the U.S. studies.

Here is the pain curve for Study 1031. At the primary efficacy endpoint of 13 weeks, which is boxed in red, there is clear separation between the placebo curve in black and the 1.25-unit condoliase curve in red. The study was positive with an effect size of 15.2 millimeters and a p-value of 0.0011.

This is the pain curve for Study 1133. This

study was also positive, albeit with a smaller treatment effect size of 7.5 millimeters and a p-value of 0.026. This is the pain curve for Study 1131. Study 1131 failed with no significant difference observed between treatment arms at week 13.

The applicant identified two primary reasons for the failure of Study 1131. They argue that the enrollment of patients without imaging-confirmed nerve root impingement may have led to reduced efficacy, which led to the applicant modifying selection criteria for Study 1133. Additionally, there was a higher baseline low back pain VAS score in Study 1131.

We interrogated the three studies independently. In the interest of brevity, I will not go through the minute details of the strategy of our interrogation, but I will note that the critical differences were in the eligibility criteria and the downstream effects on the homogeneity of the population that were enrolled.

This is the first table of the study design

differences that we suspect may have led to the failure of Study 1131. The left column contains the selection criteria followed by the three phase 3 studies. Study 1031 and Study 1131 did not have specific enrollment criteria to ensure patients had confirmed nerve root impingement on MRI. Study 1133 explicitly ensured that only patients with MRI-confirmed nerve root impingement were enrolled.

This is a table of baseline characteristics at enrollment. The two positive studies, Study 1031 on the left and Study 1133 on the right, enrolled patients with a higher rate of MRI-confirmed nerve root impingement when compared to the failed study. In Study 1131, only 27 percent of patients had MRI-confirmed nerve root impingement.

We also investigated other differences in eligibility criteria between Study 1131 and Study 1133. Study 1131 allowed for enrollment of patients with severe low back pain that was greater than the patient's radicular leg pain. This was

exclusion criteria for Study 1133. Nearly 20 percent of the patients enrolled in Study 1131 had worse back pain than leg pain. Condoliase is not intended to treat low back pain.

Study 1133 also specifically excluded patients with back pain due to non-lumbar disc herniation causes. The baseline VAS at enrollment was significantly higher for the patients in the negative study compared to the positive study. Study 1131 also allowed for enrollment of patients with comorbid chronic pain disorders that may have confounded the diagnosis and efficacy assessments of lumbar radicular pain. These included peripheral neuropathy; CRPS; lower extremity osteoarthritis; and other potential confounding chronic pain disorders. These patients were explicitly excluded in Study 1133.

Finally, Study 1131 allowed for enrollment of patients with comorbid lumbar spine disease, including spondyloarthritis, vertebral compression fractures, and severe facet arthritis, which may cause radicular pain independent of disc herniation

and limit the efficacy of condoliase. These patients were excluded from Study 1133.

Numerous subgroup efficacy analyses based on the differences in eligibility criteria, as well as other demographic and clinical factors, protocol deviations, and missing data, were performed to interrogate Study 1131. Detailed statistical analyses were unable to identify a specific cause for Study 1131 failing to meet its primary efficacy endpoint. All that can be concluded is that Study 1133 made multiple changes to Study 1131 eligibility criteria and resulted in a positive study. Given the proposed mechanism of action of condoliase, these changes seem reasonable. Confirmation of nerve root impingement is a reasonable expectation to assure diagnostic specificity and optimize potential benefit of the drug.

In summary, the applicant has fulfilled the requirement to show substantial evidence of effectiveness with the two positive adequate and well-controlled trials. The effect size ranges

from 7.5 millimeters to 15.2 millimeters, which is consistent with many approved products for chronic pain. Thus, we believe that condoliase is effective for the proposed indication of treatment of radicular leg pain associated with confirmed nerve root impingement caused by lumbar disc herniation in adults.

Now, I'm going to discuss our safety findings for condoliase. We conducted the review of safety, focusing on the major safety findings, including deaths, SAEs, and AEs leading to discontinuation. We also looked at adverse events of special interest in light of the purported mechanism of action of condoliase. Per routine, we also assess common, non-serious adverse events. Those are not the emphasis of this presentation.

This section will cover general safety. The safety data consists of those acquired in clinical studies and postmarketing safety data from Japan. This is a summary of the clinical trial safety database. There's been a total of 1,679 exposures of condoliase, with 326 patients having at least

one year of follow-up.

Throughout the safety section, I will refer to the primary safety pool, which, as you can see, included the three phase 3 studies and Study 1021. I have previously not discussed Study 1021. It was a phase 2/3 randomized, double-blind, placebo-controlled study investigating a 1.25, 2.5, and 5-unit dose of condoliase. The applicant seeks approval of the 1.25-unit dose.

After week 13, only SAEs and AEs related to the disc and surrounding areas were recorded for Studies 1021, 1031, and 1121. These adverse events included leg pain, back pain, and other adverse events related to neurological tests or the stability of the intervertebral disc and its surrounding tissues. All other controlled studies had full safety monitoring data collected based on the FDA feedback provided in 2013.

We also have over six years of postmarketing data from Japan. Condoliase was approved in Japan in August of 2018 for the treatment of lumbar disc herniation, with an estimated exposure of around

29,000 patients in Japan as of June 2024. The sources for postmarketing data include unsolicited reports, which consist of spontaneous reports, literature searches, and early postmarketing phase vigilance, which consists of alerts sent to the physician to promote adverse event reporting.

There are also solicited reports, which include the General Drug Utilization Research System, or GDURs, which is the short-term solicited follow-up, and the Special Drug Utilization Research System, or SDURs, which is the longer term solicited follow-up, which can be up to 36 months post-injection. Multiple periodic safety update reports have been submitted to the Japanese Pharmaceuticals and Medical Devices Agency, or PMDA, and there have been no updates to the Japanese package insert since its approval.

This table summarizes the major safety findings. On the left data column is the 1.25-unit dose of condoliase, while the data column on the right is the placebo/sham pooled data. The percentage of patients who died in the primary

safety pool was comparable between the active and control arms. Because it was not possible to stop dosing this product, the meaning of discontinuation for adverse events is unclear. Regardless, the rate of discontinuation was slightly higher in the control arm, while the rate of SAEs, or serious adverse events, was similar between the active and control arm.

The applicant submitted tabular summaries in four epochs, from injection to week 13, week 13 to week 26, week 26 to week 52, and week 52 and beyond. This table shows a summary of treatment-emergent adverse events in the first epoch up to 13 weeks after injection for the primary safety pool. I have boxed as significant imbalances, as they pertain to spine-related adverse events. The adverse event to back pain was reported more frequently in the active arm along with MRI and X-ray imaging abnormalities of the lumbar spine.

This is for epoch 2, week 13 to week 26. As you can see, the frequency of adverse events is

overall reduced but still a higher rate of imaging abnormalities compared to the pooled group on the right. Of note, the placebo group is not applicable, as Study 1021 and Study 1031 did not have full safety monitoring beyond week 13.

This is for epoch 3, week 26 to week 52. The imaging adverse events continue to be higher in the active arm compared to the pooled control arm, but overall reduce frequency when compared to that first epoch.

This is a summary of all TEAEs above 2 percent for the 52-week period in entirety for only the phase 3 studies for the 1.25-unit dose of condoliase versus the pooled control group. There are significant imbalances, as previously discussed, for imaging and back pain. There is also a small but higher rate of rash in the active arm, which I will discuss later in the hypersensitivity section.

Condoliase is a foreign protein administered parenterally. Intrinsically, it poses a risk for hypersensitivity and anaphylaxis. Additionally,

while condoliase can reduce disc herniation volume, it also decreases disc volume overall, which can be associated with functional and structural risks of the lumbar spine. In reviewing this application, we have coined a term to describe a group of adverse events related to the mechanical effects of condoliase on the disc called "spine-related adverse events" or SRAEs. These include axial back pain and imaging-related findings.

I will now discuss some of the measures used to evaluate the spine-related adverse events. The MRI evaluation looked at modic changes, which are structural lesions of the vertebral endplates. They are classified into three categories, as you can see in the figures on the left.

In figure A, we have type 1 modic changes, which indicate the presence of bone marrow edema and inflammation. These changes have been associated with chronic low back pain. In figure B, we have type 2 modic changes, which indicate the presence of marrow ischemia and fatty infiltration. And in figure C, we have type 3

modic changes, which indicate the presence of subchondral bone sclerosis.

We also investigated two measures of radiographic instability of the lumbar spine. The top-right figure is an example of how vertebral translation is measured, with the patient inflection and extension then subtracted to get the distance of translation. The cutoff we used was greater than or equal to 3 millimeters. The bottom-right figure is an example of how posterior angle opening is measured with the patient inflection. The cutoff we used was greater than or equal to 5 degrees.

A placebo injection was utilized in the Japanese studies, 1031 and Study 1021, with intradiscal puncture and injection of one milliliter of saline as the control. In the U.S. studies, a needle was advanced to the lumbar paraspinal musculature. The disc was not punctured, and no product was administered for the sham procedure. Placebo is a better comparator when investigating the drug rather than the drug

plus procedure, but sham may be a better comparator when investigating the totality of the treatment versus conservative care.

Discography, which includes disc puncture and injection, has been associated with acceleration of disc degeneration. The agency advised the sponsor to use a sham control prior to initiating Study 1131 to reduce the potential of iatrogenic disc damage. It is important to analyze the data in the context of what type of intervention was performed for the control group. The safety data show a higher rate of adverse events in the patients randomized to placebo instead of sham.

We viewed the disc height loss after a lumbar discectomy as a model analogous to condoliase to help guide safety monitoring of spine-related adverse events. A decrease in disc height is associated with decreased intradiscal pressure and alteration and load transfer between vertebral bodies. Disc height loss is often the index event of degeneration of the lumbar disc in

facets, which are the connected posterior joints in the vertebrae. Disc height loss can lead to degenerative spondylosis and even segmental instability.

This is the table of the onset of adverse event reporting of back pain in the primary safety pool. The adverse event of back pain was higher in the active and placebo arm when compared to the pooled control arm. The majority of back pain adverse events declared soon after the injection; in fact, the control arm had higher rates of back pain reporting after 13 weeks.

This is a table of the severity of adverse event reporting of back pain in the primary safety pool. There's a higher rate of mild and moderate back pain reporting in the active arm compared to the pooled control data. For the adverse event of severe back pain, it was relatively balanced between the two arms.

We investigated multiple imaging parameters, including X-ray measures of lumbar instability in flexion and extension as previously discussed.

Each column has a different imaging measure, and each row has a different time point of range chronologically, consisting of the studies and the primary safety pool.

On the left side of each column is the percentage for the 1.25-unit dose of condoliase, and on the right side of each column is a percentage for the sham placebo pooled control arm. The percentage of patients with vertebral posterior angle flexion greater than or equal to 5 degrees remains low and stable throughout each time point and relatively balanced with the control arm. Additionally, the percentage of patients with vertebral body translation of greater than or equal to 3 millimeters also remains low and stable throughout each time point and relatively balanced with the control arm.

This is a table of the disc height loss and endplate-related changes in the spine. Similar to my last slide, on the left side of each column is the percentage for the 1.25-unit dose of condoliase, and on the right side of each column is

a percentage for the sham/placebo pooled control group.

The first imaging measure is the total disc height loss as a percentage decrease from baseline. The disc height loss begins within the first few weeks after injection and plateaus around week 26. There is an imbalance with a larger reduction in disc height in the active arm compared to the control. The second imaging measure on the right is the percent of patients who had greater than or equal to 30 percent disc height loss. Again, this plateau is around week 26 and is more frequent in the active arm.

This is a table of the progression of modic changes. There were significantly more patients who developed type 1 and type 2 modic changes in the active arm compared to the pooled control. There were no patients who developed type 3 changes at these time points. While disc height loss progression peaked around week 26, type 2 modic changes appeared to continue to develop into the 52-week time point.

The data from the primary safety pool demonstrates that condoliase is associated with a higher rate of disc height loss, including severe disc height loss, and progression of modic changes, especially to type 1, and to a lesser extent, type 2. The clinical significance of these changes is not fully established in the literature. Multiple reviews have shown an association between modic changes and low back pain, but true causality has been difficult to establish. We did see a general trend towards less favorable treatment effect sizes for VAS low back pain for patients who developed type 1 modic changes at week 52.

We also looked at development of aberrancy in bony architecture that may occur as sequelae of disc height loss, including osteoarthritis; retrolisthesis; spondylolisthesis; compression fractures; and foraminal stenosis. The overall rate of the spine-related adverse events was comparable between the active and control arms at all time points. Additionally, there was one case of discitis in the condoliase group in the primary

safety pool, a frequency consistent with published rates of adverse events associated with disc access.

We also investigated lumbar surgery requirements after treatment. This is a table of the primary safety pool at all time points. The rate of post-treatment surgical requirement at the target level was slightly higher in the pooled control arm, and even higher when looking at the placebo-only group.

There were additionally two long-term follow-up studies that investigated spine-related adverse events. Study 10r2, which is in the first column, followed 179 patients in the active and control arms for an average of 2 years after injection from Study 1031, which was the Japanese phase 3 study, and 5 years after injection from Study 1021, which was the Japanese Phase 2/3 study. Study 10r3, which is on the column on the right, only followed patients in the active arm of Study 1031, but for an average of 10 and a half years after injection. Both studies utilized

patient interviews and imaging assessments, including lumbar X-ray and lumbar MRI.

The final lumbar surgery rate in Study 10r2 was 20.7 percent in the placebo arm and 10.8 percent in the active arm for the 1.25-unit dose. After an average of 10.5 years post-injection from Study 1031, the rate of lumbar surgery was 13.5 percent for the 1.25-unit dose, slightly higher than the rate in Study 10r2. While the sample size is modest and Study 10r3 did not follow up with a control arm, the long-term studies also demonstrated that condoliase does not appear to be associated with major progression of mean disc height loss or radiographic measures of instability.

Now, I'm going to discuss condoliase and its association with hypersensitivity reactions. Condoliase is purified from a Gram-negative rod and represents a foreign protein. We obtained a consult from the Division of Pulmonology, Allergy, and Critical Care to assess hypersensitivity and anaphylactic reactions.

This is a slide of the SMQ, or Standardized MedDRA Query, of hypersensitivity for the primary safety pool at all time points. As you can see, the rate of hypersensitivity was higher in the condoliase arm when compared to the pooled control group. The most common hypersensitivity adverse events that occurred at a higher rate compared to the pooled control group was rash; urticaria; asthma; conjunctivitis; contact dermatitis; and pruritus.

We also investigated the onset of these hypersensitivity reactions. Many of these reactions occurred within the first week, but there was a large number that occurred up to 13 weeks post-injection. A potential mechanism may be due to the poor vascularity of the nucleus pulposus, which can result in the presumed residence time post-injection being prolonged, and therefore, potentially prolonging the duration of hypersensitivity reactions.

We also looked at the severity of hypersensitivity reactions. This is a table of the

SMQ of hypersensitivity for the primary safety pool at all time points. The majority were mild to moderate with only one severe case in the primary safety pool. This severe case was for a toxic skin eruption.

In summary, condoliase is associated with a small increase in risk of mild to moderate hypersensitivity-related adverse events. Most of the hypersensitivity adverse events occurred within the first few days to weeks, but some were delayed. There were no cases of grade 3 or 4 hypersensitivity in the clinical trials. There were no cases of anaphylaxis in the clinical trials, but one case in the postmarketing data. Condoliase is also associated with severe cutaneous adverse reactions.

SCAR is a subset of hypersensitivity reactions. SCARs are rare but potentially life-threatening skin reactions often due to hypersensitivity. SCARs are a risk with many currently approved drugs, including anticonvulsants, antibiotics, NSAIDs, and

allopurinol. There are five key diagnoses, including drug reaction with eosinophilia and systemic symptoms, or DRESS; Stevens-Johnson syndrome; toxic epidermal necrolysis; erythema multiforme; and acute generalized exanthematous pustulosis.

This is a table of the number of cases of severe cutaneous adverse reactions in the Japanese postmarketing data for the system organ class of immune and skin disorders. As a reminder, there have been approximately 29,000 exposures as of June 2024. In the first column is the number of cases of SCAR, boxed in red, along with other serious skin and immune reactions. There have been 5 cases of SCAR, including now 3 cases of acute generalized exanthematous pustulosis; one case of erythema multiforme; and one potential case of Stevens Johnson syndrome.

Most of these cases declared within 1 to 2 days after injection, with a spreading rash often as the first symptom. The rashes have spread to cover a body surface area of over 75 percent in

some of these reactions. These patients were hospitalized and suffered significant morbidity, with some cases taking months to recover. Patients often required prolonged hospitalization and treatment with systemic and topical steroids, even after discharge.

In nonclinical studies, the observed endplate changes continued at the site of administration one year after follow-up. The nucleus pulposus is a poorly vascularized structure, and may potentially play a significant role in the prolonged duration of the severe cutaneous adverse reactions.

Now, I have some comments about the proceduralists and the clinical setting of condoliase administration. Interventional pain management is a highly specialized field with physicians from many training backgrounds, including anesthesiology; physical medicine and rehabilitation; interventional radiology; and many others.

There are currently no marketed intradiscal

drugs for radicular pain due to lumbar disc herniation. Technically, chymopapain is still an approved biologic, although it has not been marketed since 2001. In the past, discography and other disc access procedures like intradiscal electrothermal therapy, or IDET, were commonly performed.

These disc access procedures have seen reduced utilization over the past few decades, and this may be reflected in newer trainees who have less experience with these procedures. Additionally, disc access has many variables within the technical aspect, including needle approach and technique, imaging modality, and periprocedural medication administration.

Disc access procedures can have significant technical variability between physicians. They do require a detailed knowledge of the anatomy and significant procedural vigilance. As I previously discussed, there are many factors which can affect the benefit-risk profile of condoliase, including diagnostic specificity. Some of this will be

mitigated by labeling, but there is still a concern for off-label use, including repeat usage, which can affect the risk for hypersensitivity; administration to multiple discs, which can affect the safety profile of spine-related adverse events, especially if administered to adjacent discs; and injection outside of the lumbar spine into the cervical and thoracic spine for which the spine risk has not been assessed at this time.

Another clinical consideration is the setting where condoliase will be injected. There's a large variety of clinical settings where interventional pain physicians practice, including outpatient clinics, ambulatory surgical centers, and hospitals. Higher acuity settings will have more support staff available to manage reactions, including anaphylaxis, while small outpatient clinics may not be equipped to handle these severe reactions. Available resuscitation equipment and rescue drugs, including defibrillator and airway equipment, may also be variable depending on the setting. Crash cart availability and contents,

including resuscitation medications like epinephrine, antihistamines, and systemic steroids, may also vary.

Now, I will provide a summary of our analysis. The applicant has fulfilled the requirement for demonstrating substantial evidence of effectiveness with Study 1133 and Study 1031. Study 1133 modified patient selection criteria from failed Study 1131 to explicitly exclude patients with confounding comorbidities and explicitly enrolled patients with MRI-proven nerve root impingement. Because the presence of nerve root impingement is important for condoliase's proposed mechanism of pain relief, and its absence may indicate an alternate source for the patient's pain, MRI-proven nerve root impingement would be clinically justifiable for consideration of the benefit-risk for condoliase.

Condoliase is associated with spine-related adverse events. These risks are: one, significant reduction in disc volume and measured disc height; two, risk of increased back pain exacerbation with

most exacerbations reporting early; and three, modic changes which persist over longer term follow-up. The limited long-term, follow-up data for condoliase do not show significant progression of mean disc height loss or measures of radiographic instability like posterior angle opening or vertebral translation when compared to the control.

Condoliase has a clear risk of hypersensitivity, most commonly manifested as mild or moderate reactions. There were no cases of anaphylaxis in the clinical trials database, but one case of confirmed anaphylaxis in postmarketing. Although rare, we also know condoliase is associated with severe skin reactions known as SCARs, which can be life threatening.

Finally, I will summarize the complex clinical factors associated with potential approval of condoliase. Ensuring safety and efficacy in treatment with condoliase will depend on many factors, including patient selection; procedural skills; the ability to diagnose and manage

hypersensitivity reactions; and finally, the ability to diagnose reactions that may require hospitalization, like SCAR.

The ability to manage these will also depend on support staff and resuscitation equipment and medications in the setting of a patient with symptoms of anaphylaxis. Ensuring adequate safeguards in the clinical setting would be vital to optimizing the benefit-risk profile of condoliase. That is the end of my presentation. Thank you.

Clarifying Questions for FDA

DR. BATEMAN: Okay. Thank you.

We will now take clarifying questions for the FDA. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it will be helpful for you to acknowledge the end of your question with a thank you and the end of your follow-up question with,

"That is all for my questions," so we can move forward to the next panel member.

Are there any clarifying questions for the presenter?

Dr. Schiff?

DR. SCHIFF: Yes. Thanks very much, Dr. Sudhakaran, and just a general comment. I was very impressed by the FDA's analysis of what's a complex situation. If I could ask to take another look at slide 12 in your presentation, this is the primary endpoint showing a modest but statistically significant difference in the pain scoring at 13 weeks.

Are there any subgroups large enough to be meaningful that continue this for at least a year? I'm concerned that a temporary reduction of pain for benign disease in relatively young people is a temporary reduction.

DR. DOSHI: I'll be fielding the questions for the FDA and sending it to the appropriate respondent but, Dr. Sudhakaran, I believe you can answer this question.

DR. SUDHAKARAN: Yes. We've essentially only verified this at the primary efficacy endpoint, so the data for the 52 weeks is supportive, I would say, but it's not fully confirmed, I would say.

DR. SCHIFF: The second question, I haven't seen in any of the material, or in our discussion here, any discussion of the immune response long term to immunizing against a protein made by proteus vulgaris. For those of us on the clinical side, we mostly have some bad experiences with this organism when it causes difficult to treat and severe infections.

There's also literature on its normal presence in the gut and the implications that that's related to everything from gastroenteritis to Crohn's disease. I don't see, so far, evidence that it's made by other bacteria, but it likely is. Nevertheless, it's mostly associated with proteus and that particular species.

Is this something that needs to be of concern long term? It could be. We've just

immunized a lot of people against a nasty infection. That would be good. We also could have antibody-dependent enhancement, which would not be good during such infections, and of course the gut microbiome mystifies all of us. If you have any thoughts or suggestions about how that relates to the FDA, potentially immunizing against a particular bacterial protein, love to hear it. Thank you.

DR. DOSHI: Yes. I'll ask Dr. Paterniti from the Division of Pulmonology, Allergy, and Critical Care to talk about immunogenicity and our concerns related to that.

DR. PATERNITI: Hello. My name is Miya Paterniti. I'm the Clinical Team Leader in the Division of Pulmonology, Allergy, and Critical Care. I think it's an excellent question. We did look at the population in terms of risks, if we could figure out if there were patients with histories that put them at higher risk. We did not.

I do want to note, apart from the question

you asked, this product also does contain PEG, so in the product label it would obviously state that, and it would be contraindicated for patients who had a known allergy to, obviously, the product or to any of the excipients, which would include PEG. So that would be communicated to prescribers and patients. But in terms of the risk for protease, we didn't see anything specific in the patient populations that were included in the clinical trials.

DR. BATEMAN: I'd like to ask a question, if you could pull up slide 54. While that's coming up, this is the slide that shows the frequency of the hypersensitivity reactions. So my question is, what is the confidence that there's comprehensive capture of the severe cutaneous adverse reactions, the SCARs? There are 29,000 exposures. How confident are we that we have full capture of SCARs in that population?

DR. DOSHI: Yes. Dr. Sudhakaran can speak to that.

DR. SUDHAKARAN: I'll argue that the data

that we have is based on the Japanese postmarketing data, and there's a fraction that are solicited versus unsolicited. The solicited data I would argue is probably a little better because it's actively following up with these patients, and the initial follow-up is, I would say, more active than the longer term follow-up.

So your question of do we know for sure that we've caught all these SCARs, I would say the answer is no. The rate is relatively infrequent based on the data that we have, but we can't be certain that we missed one case based on this reporting.

DR. BATEMAN: Okay. I guess a conservative estimate would be, then, that 1 in 6,000 administrations result in a SCAR; and these are very serious reactions, obviously, as you pointed out. Where does that observed rate fall relative to other drugs that have these types of hypersensitivity reactions, lamotrigine or --

DR. DOSHI: Yes. It's a difficult question to answer, but going back and looking at prior

data, this is comparable to other approved drugs. I don't know, Dr. Sudhakaran, if you had any additional comments.

DR. SUDHAKARAN: Yes. We saw quite a range of frequencies. I know allopurinol was much more common. I think it's one of the most common offenders for SCAR. Some of the other ones like lamotrigine and these other drugs may be a little bit less frequent. So I would argue it is of significant concern with these other drugs, so I would argue that it is of significant concern for this drug.

DR. BATEMAN: So the frequency is in the same range as allopurinol and lamotrigine.

DR. SUDHAKARAN: Allopurinol was on the high end. I would put it somewhere in between, yes.

DR. BATEMAN: Dr. Stojanovic?

DR. STOJANOVIC: I second Dr. Schiff. It's excellent and answers the study. Thank you. I have several questions. One is technical, the first question. Thank you for pointing that injection in disc is a complex procedure, and it's

been out of favor because there's this disc program and several hundred of disc and intradiscal procedures.

Some things to be thought about are, if you have disc herniation that doesn't have radial tears -- so it doesn't have a tear, which is a perfect candidate -- it's a little surprising that even those 29,000 people haven't been reported of acute increase of radicular pain with putting 1 cc of any kind of volume in disc. It's very unusual that there has never.

So physicians who will be performing this procedure, they should be informing patients that the pain might get worse. Some of these people might have to go to surgery right away because the disc herniation might worsen. So that's my first question, that something should be taken into account.

DR. DOSHI: I'm sorry, Dr. Stojanovic. What was the question; whether that should be taken into account, the potential for increased --

DR. STOJANOVIC: Yes. It should be looked

at, and it's surprising that we didn't hear that data.

DR. DOSHI: Yes. I would defer to the applicant regarding whether they looked at that particular data acutely, but what I will say is that it's certainly something we can take into consideration as we're making our decisions.

DR. STOJANOVIC: The second --

DR. BATEMAN: Actually, can we just limit to one question since we only have 10 minutes?

DR. STOJANOVIC: Yes.

DR. BATEMAN: Okay. Dr. Sprintz?

DR. SPRINTZ: Hi. Michael Sprintz. I just had a quick question. On slide 58, we talked about a potential for a high rate of off-label usage. And one of the other things that we didn't talk about specifically was the use of contrast, and I can imagine that there are going to be some practitioners who are going to consider either mixing with contrast or using any contrast. I know with chymopapain, there was an increased risk of problems when mixed with contrast. So I was

curious if there's any contraindication for this product with contrast dye.

DR. DOSHI: Dr. Sudhakaran can answer that.

DR. SUDHAKARAN: Yes. Condoliase is not intended to be mixed with another drug. You shouldn't be mixing with contrast. You shouldn't be mixing with antibiotics. I know some people do intradiscal antibiotics.

DR. BATEMAN: Dr. Reich?

DR. REICH: Jeff Reich, Sparian; a couple questions. Do I only get one?

(Dr. Bateman gestures yes.)

DR. REICH: Okay.

(Laughter.)

DR. REICH: Let me go for the main one. If you could put up slide 12, and then 13. That's 1133, and then go to 1131.

The thing that pops out at me is the error bars and the huge variability between those studies. Usually what I think of when I see that is study conduct, variability from study conduct. So maybe you can comment on how you interrogated

1131 with respect to sites, variability by sites, number of sites, and so forth.

DR. DOSHI: Yes. We'll have Dr. Wang answer that question.

DR. WANG: This is Sue-Jane Wang from the FDA. The slide here might be a little misleading because this slide here is only looking at the mean worst leg pain, whereas the other two figures that you saw, they're showing the change from baseline at week 13, at each of the visits. So, if we convert this figure to an equivalent of the other two figures, you don't really see that huge variability that you're seeing here. I don't know if it's possible. We do prepare a slide that we can share with you, but it's probably not required unless everybody wanted to see that slide.

DR. REICH: Okay. Because in table 21, in the in the sponsor's presentation, I think you do have the comparable least-squared mean change from baseline, and the 95 percent confidence intervals look to be very comparable to what you're demonstrating here, and much wider than what we've

seen in 1031 or 1133.

DR. WANG: If we can go to the previous slide, you see here this is the least square mean change from baseline. That's the Y-axis. You're comparing the change from baseline.

DR. REICH: No. I'm also thinking of table 21 in the sponsor's briefing book --.

DR. WANG: I don't have the sponsor's table to rely on.

DR. REICH: -- and the confidence intervals; and the least-squared change from baseline --

DR. WANG: Yes.

DR. REICH: -- also look variable.

DR. WANG: For Study 1131 --

DR. REICH: Correct.

DR. SUDHAKARAN: Which page is that?

DR. REICH: Sixty-seven.

DR. SUDHAKARAN: Oh, 67.

DR. DOSHI: So as we're bringing that up and looking, just to speak directly to your question about study conduct, we did do several analyses looking at protocol deviations, missingness of

data, making sure that the study eligibility criteria, the inclusion/exclusion criteria, that those were all examined in our analyses for both 1131 and 1133, and we didn't find any evidence suggesting --

DR. REICH: And concordance by site?

DR. DOSHI: I don't have that information.

Dr. Wang, we looked at concordance by site specifically?

DR. WANG: Not really. We didn't further look into that, but the sponsor might have that particular data by site. But we just want to point out that the kind of variability in Study 1131 is actually not that different from the other two studies, and that information is included in the eventual FDA review that will go public.

So in other words, the variability concern that you see in that slide is not an accurate representation because they're only looking at the endpoint data rather than the change from baseline. That difference is what the primary efficacy endpoint is. I don't know how I can project my

particular slide to everybody that can see clearly that's not a concern.

DR. REICH: Okay, and I won't belabor it. Forget that slide, then. Just on table 21, it seems to be an apples to apples.

DR. WANG: Can that slide be pulled up?

DR. BATEMAN: We can have the sponsor pull that up, maybe.

DR. REICH: We can table it for later, if you'd like, sure.

DR. BATEMAN: Okay. Let's do that.

Oh. Do you have it?

DR. STAUFFER: We just pulled it up there. We'll bring it up again.

DR. REICH: That is the least-squared mean change from baseline; right?

DR. WANG: Right. So, if you look at the least-squared mean change from baseline, that variability in the condoliase arm is 2.11 versus 3.36. That's the standard error.

DR. REICH: Yes.

DR. WANG: That captured that variability,

yes. So the question is?

DR. REICH: And the 95 percent confidence intervals --

DR. WANG: The 95 percent confidence interval of the difference between the two study arms --

DR. REICH: -- compared to 1031 and 1133 --

DR. WANG: Right.

DR. REICH: -- looks to be much wider. So the question is about the variability in 1131.

DR. WANG: We have all those actual numbers. We do not see that it has a much larger variability. We did not see that.

DR. REICH: Okay.

DR. BATEMAN: So maybe this would be a good point for the sponsor to pull up the data that we had requested prior to the break on the subgroup of patients that had MRI-confirmed impingement in 1131.

DR. STAUFFER: We'll have Ben Vaughn speak to you on that one.

MR. VAUGHN: We do not have that quite

ready, and we will --

DR. BATEMAN: After lunch.

MR. VAUGHN: -- pull it up after lunch.

DR. BATEMAN: Okay. Perfect.

MR. VAUGHN: But, yes, that would be a good point to see this, and see it relative.

DR. BATEMAN: Yes.

MR. VAUGHN: Exactly.

DR. BATEMAN: Okay. We'll do it after lunch.

Dr. Kennedy?

DR. KENNEDY: Like others, I want to commend the FDA on a spectacular presentation and condensing a lot of really hard data. My question -- and I apologize if I missed this detail -- is, the people with flares and low back pain were categorized into mild, moderate, and severe. Do we have a VAS number for that to allow for apples to apples comparison? What thresholds were used to define mild, moderate, and severe on a VAS scale? Thank you.

DR. SUDHAKARAN: This is Dr. Sudhakaran.

Back pain adverse event reporting was based on the CTCAE version for adverse event reporting. It was not based on a VAS score; it was rather based on ADL functionality limitations. So mild was mild low back pain; moderate was certain ADLs limited; and then severe, or grade 3 or grade 4, was a significant amount of ADL limitation.

DR. KENNEDY: So just to make sure I'm clear, our primary outcomes in the leg pain reduction were a 7.5 VAS scale reduction, which I think most would count as mild. We don't have a true apples to apples comparison for that group that had an increase in low back pain; correct?

DR. SUDHAKARAN: Sorry. Are you asking for the mean back pain VAS score for that group that had adverse events, or --

DR. KENNEDY: That may work for it. I was just trying to figure out -- what I'm trying to get at is are we substituting -- I get people, and sometimes their leg pain will be better and their back pain is worse, and their overall not doing better. And that's what I was trying to figure

out, how is that relating to this, and just had a hard time with the mild, moderate, and severe.

DR. SUDHAKARAN: Yes. I'm not sure if the data exist for that split but, in general, the point estimates did favor a reduction in low back pain at week 52.

DR. KENNEDY: Okay. Thank you. That's very helpful.

DR. BATEMAN: Okay. Thank you.

We will now break for lunch. We will reconvene again in this room at 1:15 pm Eastern Time. Please take any personal belongings that you may have with you at this time. Panel members, please remember there should be no chatting or discussion of the meeting topics with the other panel members during the lunch break. Additionally, you should plan to reconvene at around 1:10 to ensure you're seated before we reconvene at 1:15. Thank you.

(Whereupon, at 12:15 p.m., a lunch recess was taken, and meeting resumed at 1:15 p.m.)

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

(1:15 p.m.)

Open Public Hearing

DR. BATEMAN: We'll now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, 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 applicant. For example, the financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the

committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

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 considerations 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 for today is that this open public hearing be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect; therefore, please only speak when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, please step up to the podium and introduce yourself.

(No response.)

DR. BATEMAN: Okay. We'll move on to

speaker number 2. Please unmute and turn on your webcam. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have five minutes.

MS. CONTE: Hi. Good afternoon. My name is Emily Conte, and I served as a study coordinator for the SKK protocol at Dr. Patel's site, Conquest Research, in Winter Park, Florida. I do not have any financial relationships with the sponsor, as well.

As a study coordinator working on this trial, I was responsible for numerous tasks, which included assisting with data entry and conducting patient visits. Needless to say, I had a first-row seat to the day-to-day conduct of this trial. The SKK protocol holds a special place in my heart for many reasons, but most importantly, this trial is meaningful to me because of the profound impact it had on patients' quality of life.

Our team would first meet patients for a prescreening visit in order to learn more about the

patient symptoms and see if they would be a good candidate for the trial. In our waiting room at the clinic, it was often easy to tell who was here for the SKK study; often, pain was written on people's faces. They found it difficult to get comfortable in the waiting room chair, and then when it was time to stand to come back for their appointments, it was no easy feat.

Once a subject was deemed eligible, the patient would either receive condoliase or the sham. Our team enrolled over 60 patients into the SKK protocol. There are many patients that come to mind who had a positive response to condoliase; however, I would like to specifically discuss two patients.

When the first patient came to us, they were at risk of losing their job. Their sciatica pain was severe enough that they frequently missed work due to their pain. I remember sitting with that patient at their week 52 visit, and they were so thankful that they decided to participate in this study. They recalled almost not being able to walk

into our office for that prescreening visit the year prior; and at the time of the week 52 visit, their pain had subsided almost completely and were excelling in their career.

Similarly, the second patient was struggling in their career as well. They worked as a car salesman, and they were consistently on their feet. The patient's severe sciatica pain began to take a toll on them, both physically and emotionally. After the injection, the patient's demeanor totally changed. The patient lit up any room they were in and would often dance during their visits to show off the improvement in their sciatica pain. Standing for long 8-hour days was also no longer an issue.

I am thankful to have witnessed the impact condoliase had on the patients that came to our clinic. The positive impact is a testament to the need for non-surgical options in treating lumbar disc herniation and sciatica pain. Thank you for your time.

DR. BATEMAN: Thank you.

Speaker number 3, please step up to the podium and introduce yourself. Please state your name and any organization you are representing for the record. You have five minutes.

DR. PATEL: Good afternoon, members of the Anesthetic and Analgesic Drug Products Advisory Committee. My name is Anand Patel. I serve as the Chief Medical Officer for Conquest Research, which is a fully dedicated clinical research site network headquartered in Winter Park, Florida. I have no financial relationship to disclose. I am a board certified physician in anesthesiology with a subspecialty certification of pain management, and I've been a practicing clinician for 20 years.

Relevant to our discussion today, our site was the highest enrolled in the Seikagaku 6603-1133 study, which was a phase 3 study evaluating the efficacy and safety of condoliase as a potential treatment option for the treatment of patients suffering from sciatica due to lumbar disc herniation. This innovative treatment has transformed the management of a debilitating

condition, offering the potential for relief and improved quality of life for countless patients.

Lumbar disc herniation affects a significant portion of the population with symptoms ranging from mild discomfort to severe pain disability. This combination of physical symptoms, impaired quality of life, mental health burden, and economic impacts on patient livelihood all are justification for seeking safer and more efficacious treatment options for this condition.

Currently, there is a large gap in the treatment options available for this medical condition. Due to a combination of side effects, efficacy, or lack of efficacy, and risk associated with the current standard of care, there remains a need to find an effective minimally invasive treatment option for these patients that targets the underlying pathology while carrying a low risk; hence, the importance of condoliase as a potential solution.

Condoliase is a drug which is administered via a minimally invasive procedure, where the drug

is injected into the impacted disc. The drug selectively degrades glycosaminoglycans and the nucleus pulposus of intervertebral discs. This reduces disc pressure, alleviating nerve compression and potentially reducing nerve pain symptoms. Because condoliase is administered via minimally invasive injection, it provides an effective alternative to surgery without the carried risk. In addition, the enzyme acts directly on the affected disc, minimizing systemic side effects and targeting the affected pathology.

The phase 3 study has already been conducted in Japan, demonstrating efficacy and safety of the drug. That drug is currently commercially available in Japan and has been subject to substantial postmarket analysis, which supports substantial evidence of significant pain relief in patients with lumbar disc herniation and a favorable safety profile with minimal, at best, adverse effects in routine clinical settings.

On a personal note, we were privileged to enroll 69 subjects in the phase 3 U.S. study. We

were the highest enroller. Repeatedly, we would witness patients who would come in with debilitating pain, impacting them both physically and emotionally while compromising their livelihood. These patients had exhausted conservative therapies and were opposed to surgical intervention due to perceived risks.

On numerous occasions, our patient volunteers returned for their follow-ups 1 to 4 weeks after treatment, noting remarkable improvement in their pain and function, a dramatic turnaround from their pretreatment status. As neutral observers, we would commonly notice a dramatic improvement not only in pain-focused measurements but also an affect and mood. Seeing this as a clinician was rewarding, knowing such a simple and low-risk treatment could be so impactful in altering these patients' lives.

In conclusion, condoliase represents a significant advancement in the treatment of lumbar disc herniation. It addresses the limitations of traditional therapies, providing patients with

relief, functionality, and help for a better quality of life. Improving this drug will improve accessibility for patients while reducing economic burdens on the patient, the healthcare system, and the workforce. I urge this committee to recognize the importance of making condoliase widely accessible to those who need it. Thank you for the opportunity to present this testimony.

DR. BATEMAN: Thank you.

Speaker number 4, please unmute and turn on your webcam. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have five minutes.

MR. BUSSEY: Good afternoon, and thank you for the opportunity to share my experiences. My name is Carlos Bussey, and I'm a clinical trial coordinator at Vantage Clinical Trials. We're located in Tampa Bay, Florida. I have been working in clinical research since 2006, and I do not have a financial relationship with the sponsor.

Over the span of 10 years, starting in 2013

and culminating in March of 2023, I had the privilege of coordinating three pivotal clinical trials for this therapy. These trials were conducted across seven interventional pain management medical practices in Tampa Bay, where I witnessed firsthand how this therapy transformed patients' lives, offering new hope and alternatives to those suffering from lumbar disc herniation and sciatica.

Many of the patients I encountered were in significant distress, experiencing severe pain, reduced mobility, and quality of life. A significant number of participants in the first two studies were on daily opiate therapy, as this was permitted within the protocol at the time. These patients often expressed frustration with the limitations of opioids, including dependency and diminishing effectiveness. Additionally, many patients had undergone epidural steroid injections, which typically provided only temporary relief lasting about 6 months, leaving them searching for long-term solutions.

As an example of a patient, we had a male patient in his late 30s, and he shared how the trial completely changed his life. Before joining the trial, he was a regular pain patient in our practice, relying on opiates to manage his condition. After treatment with condoliase, he was able to quit opiates and reclaim his independence, and take on simple, profoundly meaningful activities like being able to pick up his daughters again.

Another example was a yoga teacher in her late 40s who had to give up her daily practice to debilitating leg pain, which greatly affected her livelihood and mental well-being. Following treatment with condoliase, she not only returned to her practice but also resumed teaching classes, describing it as a gift that gave her her life back. Witnessing patients regain independence and hope was incredibly moving. For patients who had been reliant on opioids or had experienced cycles of temporary relief, the trial offered a renewed sense of control over their lives, fostering

optimism about their futures.

Surgery for lumbar disc herniation is often seen as a last resort, not only because of its risks but also due to its significant financial burden. The cost of a discectomy surgery can range from $15,000 to $50,000 or more in the United States, depending on the patient's insurance and healthcare setting. Many patients on the trial cited these costs as a major barrier to pursuing surgery. Additionally, we also saw many patients that underwent discectomy surgery, ending up back in pain management within 6 to 12 months.

These challenges, combined with the temporary relief from epidural steroid injections, underscore the need for condoliase as a better, less invasive, and cost-effective solution. Our investigators firmly believe that condoliase could serve as a viable treatment option prior to surgery, potentially sparing patients from the financial and physical toll of surgical intervention.

While surgery remains a viable option for

some, the recurrence of pain in many discectomy patients and the high financial and physical cost of surgery underscore the importance of having alternative therapies like condoliase. It empowers patients and clinicians to make more informed individualized treatment decisions. Thank you for your commitment to advancing treatments and for considering these real-world experiences as you evaluate the path forward.

DR. BATEMAN: Thank you.

Speaker number 5, please unmute and turn on your webcam. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you're representing for the record. You have five minutes.

MS. CLEMENTS: Good afternoon, everyone, and thank you for allowing me the opportunity to share my testimony today. A little bit about me, my name is Retta Clements, and I'm 65 years old. Currently, I reside in Cypress, Texas, right outside of Houston, Texas. I have one child, a beautiful daughter who's married with three

beautiful granddaughters that live about five minutes away from me.

I currently work from home as a property casualty agent. I had my first experience with what I know now is radicular leg pain caused by lumbar disc herniation about 4 years ago. I just woke up one day, with no prior signs nor symptoms, with excruciating pain. To give you an idea of the level of pain I was experiencing, it was worse than labor pains. At that time, I had no other medical issues, nor was I taking any medications, so I had no idea what was causing so much pain to me.

Hoping to avoid going to the doctor, as well as hoping the pain would just go away, I started Googling my symptoms online. Everything seemed to be pointing toward a sciatic nerve issue. The pain gradually became so intense, I decided to just go ahead and schedule an appointment to see my doctor. The doctor asked several questions, took X-rays, et cetera. The ending result was I was basically advised that I had a herniated disc. She prescribed two types of medications, stating that

should help.

About a week I later, I realized the medication just was not working for me. I then contacted her again, and then she suggested that I consider seeing a specialist to get other options and possibly even discuss surgery. I knew immediately that that was not the route for me, especially not at that time. You see, at that time, I was self-employed and running a funding business.

With each episode, the pain seemed to intensify. At that point, nothing seemed to help. I found myself learning to tolerate the pain better and doing my best every day to just get through. I just waited for the pain to subside, which lasted a week or two during each episode. Fast forward to the very last episode; by this time, I started to consider surgery, believing that, at that point, the surgery might be my only option, as the pain was becoming almost completely debilitating at that time as well.

Admittedly, in desperation, I started taking

Tylenol PM to dull the pain and get some sleep in between. One day as I woke up in a fog and still in pain, then about 2 months in, I knew I had to do something else to help myself because what I was doing just wasn't helping. I started researching online again, desperately seeking an alternative to surgery or going to a specialist. That is when I discovered that Conquest Research was conducting a study for experiencing radicular leg pain.

At that time, I had low expectations of their ability to help, but I knew that it was something that I needed to at least explore, so I completed the required online information, and a few days later they reached out, and I was scheduled an appointment. As a result, they decided that I would be a good candidate, and I immediately agreed to become part of the research. Fast forward and later, the same day of the injection, I went to an outdoor concert in my community. I danced for hours. The very next day, I went to Universal Studios and literally walked around the park, and enjoyed every moment of the

8 hours that I spent there with my cousin.

It has now been about about 3 years since I received the injection. I've had no leg pain since. I'm so very thankful to God, to Natalie, and the entire research team. Now, I can continue to do the things that I really enjoy doing, such as spending time with my family, my friends, traveling, and a whole host of other things that I enjoy doing. So as you consider your decisions today, I would ask that you remember my story. It's a story of so many other people like me who are suffering and looking for other options to surgery. Thank you so much.

DR. BATEMAN: Thank you.

Speaker number 6, please unmute and turn on your webcam. Will speaker number 6 begin and introduce yourself? Please state your name and any organization you're representing for the record. You have five minutes.

(No response.)

DR. BATEMAN: Speaker number 6.

(No response.)

DR. BATEMAN: Okay. We'll move on to speaker number 7.

Speaker number 7, please unmute and turn on your webcam. Will speaker number 7 begin and introduce yourself? Please state your name and any organization you're representing for the record. You have five minutes.

MR. HYLTON: Hello. My name is Ian Hylton. I'm a 33 year old from Indianapolis, Indiana, and I have no financial disclosures. My wife and I recently moved in to help care for my mother, who has advanced stage relapsing-remitting multiple sclerosis. I'm a program manager for a hospital working in behavioral health, and I manage a team of remote clinicians. Today, I'm here to share my experience participating in the clinical trial for condoliase and how it changed my life.

In March 2019, my wife and I were in a car accident. We were struck in the back driver's corner of my vehicle, and the impact hit so much that it spun us 180 degrees. I felt shaken but not injured enough to go seek medical care. So, fast

forward to November 18, 2019, a few months later; I stood up from my desk at work, stretched, and was struck with a sharp, searing pain radiating down my back and my leg. I ended up lying on the floor of my office trying to ease the pain, but it only got worse.

I drove home hunched over, barely managing the 3 flights of stairs to my apartment before collapsing. By that night, I ended up walking to the bathroom with the help of my wife. I couldn't do it by myself. My body had contorted to compensate for the pain, leaving me bent and crooked, and that night I laid in bed wondering how I would continue living if this level of pain became my future.

The next morning, my wife wheeled me into the ER because I could barely walk. I was given pain medications and muscle relaxers, but received no scans or imaging, just a diagnosis of acute back pain not caused by sciatica, and was discharged with instructions to alternate heat and ice and walk it off. A $2600 hospital bill later, I still

had no answers.

Desperate for relief, I tried everything I could afford: back braces; compression wraps; pillows; Aleve; and even CBD. Nothing worked. Any misstep, no matter big or small, could send a jolt of pain down my back and leg. Then one day, I saw an ad on Facebook for a clinical trial for sciatica. I figured why not, and I filled out the application. Before I knew it, I was enrolled in a double-blind clinical trial for condoliase.

From the start, I was amazed by the level of care. Through the trial, I finally got answers. MRI scans revealed a severe herniated disc compressing my nerve and causing my debilitating sciatica pain. As part of the trial, I received a one-time injection of condoliase directly into my herniated disc. Almost immediately, I felt slight relief, and over the next few weeks, I carefully followed the trial's guidelines, avoiding any jarring movements and letting the treatment work. By the 4-week mark, I was about 40 percent better, and at 6 weeks, I was 80 percent better. Over

time, I improved even more, and by the end of the trial, I had regained 95 percent of my health.

For months, I approached my recovery cautiously, afraid to push my back too hard, but with time, I began strengthening my core and working with a chiropractor. I now confidently say that my back is stronger than ever, and the timing couldn't have been more important. As now my mother's full time caregiver, I regularly have to move or lift her when she falls or struggles from weakness. Thanks to condoliase, I can lift her 135 pounds and manage her care without fear of reinjuring my back. Whether I'm moving furniture, working out, or supporting my mom, my back holds strong every time.

Condoliase didn't just relieve my pain, it gave me my life back, and I'm forever grateful for the strength, stability, and hope it restored, allowing me not to just survive but to truly thrive again. Thank you for my time.

DR. BATEMAN: Thank you.

We'll move on to speaker number 8.

Speaker number 8, please unmute and turn on your webcam. Will speaker number 8 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have five minutes.

MS. KUCK: Hello. My name is Tiffany Kuck. I live in Dayton, Ohio, and I am 38 years old. I do not have any financial relationship to disclose. I am married, and I have three little girls: Madeline, 5; Caroline, 4; and Alexandra, almost 2. I'm the Director of Population Health at McGohan Brabender, an employee benefits organization. Much of my job entails traveling to meet with clients to help engage their employees in population health programs, such as establishing a relationship with a PCP and understanding their biometric risk factors.

When the severity of my back pain happened, my life changed. I could not travel due to the lengths of time sitting in the car. I could not stand to present at employee meetings. I could not hold my, at the time, 3-month old baby. My life

was shattered. When I first began to experience leg pain, it was a 10 out of 10 excruciating pain experience. The entire left side of my calf was numb all the way up to my lower back. I was driving when I first experienced it and had to pull over. My husband had to pick me up from a Kroger parking lot to drive me directly to the ER.

I was just returning back to work after maternity leave. I had a 2 year old and a 3-month-old baby at the time. I could not lift either of my little girls. I had to stop breastfeeding right away because I couldn't sit and have her on my lap. When she needed a bottle, I had to prop her up on a pillow to feed her that bottle. When she was crying, my husband had to take care of her. At night, when she needed to go into the crib, my husband had to put her in there. My husband had to make dinner and do dishes because it was difficult for me to stand longer than 5 minutes. Thank the Lord I had a wonderful husband who was there by my side and holding everything down so I could take care of my body for

my future.

I did do digital physical therapy, and that definitely helped get out of a critical 10 out of 10 pain level, but I would say my pain scale was still regularly between a 7 and 9 on a daily basis. I knew I couldn't go on forever like this and needed to find another option.

When I visited my first orthopedic doc, he said back surgery right away. I said, "I'm a mid-30 year old with little ones. That cannot be my only option." I found another orthopedic doc for a second opinion. He said if I could get through these few months of pain, complete physical therapy, "I think you can get beyond back surgery, but it will take time and work." I was up for that. I didn't want back surgery.

During that time, I was doing a lot of research on ways to address pain without surgery. Through social media, I learned about a trial for the therapy you are reviewing today. I called and reached out to learn more about it because I was very interested. I loved the idea of the approach

and not going under a knife. I hope to understand a little more about why this happened and how to make changes to feel better. I learned a lot from working with Dr. Mehta about this isn't one thing that I did wrong but more of a buildup over time. Dr. Mehta was very compassionate, kind, relaxed, and knowledgeable. I am grateful to him for helping me get where I am at today, physically and mentally.

I entered the trial, and thanks to condoliase, I can now lay on the floor to play with my kids, pick them up when needed, drive in the car long distance to meet my clients and their employees, and most of all, I feel healthy and happy. Surgery can't be our only option. Every person is in a different place, and their situations are different. I am grateful to have had a different option, and pray that anybody in my situation -- mid 30s and a new mom -- to be able to avoid surgery. Thank you for your time today and allowing me to share my story.

DR. BATEMAN: Thank you.

Speaker number 9, please unmute and turn on your webcam. Will speaker number 9 begin and introduce yourself? Please state your name and any organization you're representing for the record. You have five minutes.

MS. SORRELL: Hi. My name's Michelle Sorrell. I have no financial disclosures. I'm 47 years old, married, and I have three daughters. We live in the Cincinnati, Ohio area. I've been a pediatric nurse for 23 years. As a pediatric nurse, I spend a lot of time on my feet, as you can imagine, and outside of work, I live a fairly active lifestyle.

Today, I'm here to share my experiences with the condoliase clinical trial. In early 2021, I would notice I would wake up early in the wee hours of the 5:08:15 [inaudible - audio gap] -- event or injury. My daily routine was to wake early in the morning and go to the gym before work. I started noticing certain exercises at the gym would cause shooting pain from my lower back down my right leg; and as many like to say, nurses are the worst

patients, so I didn't seek care, refused advice of friends and colleagues who suggested to try muscle relaxers, steroids, or surgeries. I didn't feel like any of those were good options.

So, I just kind of adapted by avoiding exercises that caused my pain. But eventually, I noticed I would start to have pain radiating down my right buttock into my right leg if I even sat or stood for long periods of time. I started taking ibuprofen before bed just to get any sleep at night, and then again in the morning to get through my work day.

Then one day, I was walking in Walmart, and I picked up a few items, and suddenly this pain struck. It felt like a shock of electricity shooting down my right leg. It was so bad, it knocked me to the ground. I got up as soon as I was able to recover and was pretty embarrassed, thinking I was now one of those kind of people at Walmart.

So, the next day I made an appointment with my local physical therapy clinic. I discussed the

symptoms with a physical therapist and started physical therapy 2 times a week, with regular stretching added to my usual gym routine. The physical therapist also instructed me to avoid exercises like running, squatting with weights, and basically anything that could compress my spine.

After several months of physical therapy, my pain had not improved at all. I was squeaking by with 4 hours or less of sleep at night because the pain would just keep me up. I often felt tired because I wasn't getting enough sleep. We bought a new mattress that had an adjustable frame. I started sleeping at zero gravity, so my legs were elevated, which provided a little relief and allowed me to get a few hours of sleep, but I was no better.

I had pretty much stopped trying to take ibuprofen or Aleve because it wasn't providing any relief, so I figured at this point it was doing more harm than good. I was very consistent with my physical therapy but, again, still not improving. I was getting so frustrated. The sciatic pain took

away things I took for granted, like sleeping all night, or bending down to pick something up, or even standing in one place for a period of time. I couldn't do any of those things without bouts of extreme pain. I went from one day running around to the emergency department caring for patients and taking my dogs on runs, to suddenly not even being sure if I would even be able to continue as a nurse if this pain continued to progress.

The pain made me feel helpless, old, and cranky. My daughters would see me in pain and always had different suggestions. And then one day my middle daughter said, "You should sign up for the sciatic pain study," she had seen online. And I thought, "I'm so desperate I'd try anything at this point," so I called to express my interest. I qualified for the clinical trial; then working in healthcare, I have pretty high expectations, and this clinical trial more than met them. The study coordinator and physician were professional, empathetic, and respectful of my time.

The study provided free-of-cost imaging, and

the MRI confirmed what the physical therapist suspected. I had a herniated disc compressing on my sciatic nerve. I continued with the trial, which entailed documentation of my pain and regular follow-up exams with the doctor. Eventually, I received an injection as part of the clinical trial. The study was double blinded, but I was one of the lucky ones to receive the medication. I immediately felt some relief. My pain went from a 7 to 8 out of 10 to a 5 out of 10. Within a month, I was a 2 out of 10, and I was so happy to get back to living my life.

As you consider your decision today, I would ask you to think of all the people out there like me who were suffering and want another option to surgery. Condoliase provides a minimally invasive option to cure my sciatic pain, and it was life-changing. Thankfully, I'm now sleeping 8 hours each night. I can run again. I regularly work out in the gym 6 days a week, and I'm so thankful I was able to be part of this clinical trial. Thank you so much for your time and

consideration.

DR. BATEMAN: Thank you.

Speaker number 10, please unmute and turn on your webcam. Will speaker number 10 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have five minutes.

MR. SELTZER: Good afternoon. My name is Mark Seltzer. I have no financial disclosures or obligations for this study. I'm a proud father of two middle-school-aged boys and a husband to my wife of more than 17 years. I'm a commercial real estate developer. We build large residential office, lab, and hotel projects. As the managing director of our firm, being sick, hurt, or unable to work effectively puts a severe strain on our business. We have employees who have families that are counting on me to run business; investors who have invested in our projects, including some individuals; and then also large major insurance companies and pension funds.

I've been an active person my entire life.

In my 20s and early 30s, I did what I could to keep in shape mentally and physically. Most of my exercise then was playing basketball after work and various weekends, men's leagues, and otherwise. One night when I was around 35, I fell awkwardly and knew instantly I had my first ever real injury. After not being able to move much without pain, I learned I had a herniated disc in my back. I was out of work for about a week, but little did I know that was only the beginning.

In a moment, I went from being an active, vibrant, young adult, proud father with a promising career, to someone who struggled to shower without a shower seat and who needed to leave early in the morning for work because it took me so long to walk from my parking spot to my destination. Of course, there were moments where I wasn't in the middle of a flare-up, and my life felt normal for a bit, but even then, I couldn't carry my boys in their car seats or push them in the stroller. The strain it put on my marriage and me mentally was extremely taxing.

I tried everything to get better, physical therapy to meds. The steroid shots would work periodically, provide some relief for short periods of time, and in some cases, they would work, and in others, not at all. Unfortunately, the nerve medicine or the opioids were a real problem for me. They greatly affected my cognitive abilities and my memory. My job has far too much risk for error for me to be cognitively affected, and therefore I couldn't take those meds and work.

Early on, surgery was presented as an option, but for those who are not familiar with back surgery, it seemed daunting and extremely scary. I searched for other options, and each time the doctors told me there was only surgery to have my life back. I was devastated that my life came down to the fact of the decision to have surgery or no quality of life to be able to enjoy my wife and my kids.

Two years later, then in August of 2015 at my best friend's wedding, I gave the best man speech. Later that night, all of the groomsmen and

our friends celebrated back at a friend's house. Listening to them all enjoying life in their mid 30s while I was laying in another room on a floor in absolute agony was one of the worst nights of my life. I couldn't move without any pain. I couldn't lay comfortably, and that night I went home again, spent another night crying to my wife about what my life has become, and decided to get surgery.

I woke up from surgery, and I knew it worked, but I didn't bounce back right away. In fact, I was in such bad shape for so long, I was very hesitant to do anything. The experience of the previous 2 years really took its toll on my body. My hips were a mess, areas of my back were severely out of alignment, and mentally I was a different person. Fortunately today, some 10 years later, I'm an avid golfer, although I keep my swing speed very, very low, which I would need another 5 minutes to talk about my disappointment through that. I'm a loving husband and father. Unlike when my kids were babies, I can carry them to bed,

although they're much heavier, and I even play one on one, only to three; I still do win, though.

Looking back, I looked for an alternative to avoid surgery, and if there was a drug that could have helped, I would have started it immediately. Even today, the idea of not having to get surgery and not putting the 2 years of irreversible strain on my body gets me emotional. At the very least, I was able to resolve my herniation; however, it put a great strain. I'm certain that today, without those 2 years of stressful conditions on my body, I would be playing basketball, probably even games to 11, today with my boys.

Candidly, for what it's worth, having thought about those thoughts and hearing some of these other patients expressing their thoughts on this trial, it seems like an absolutely incredible opportunity for those to experience what I was not able to experience and for what I had to endure. Thank you all for the work that you do and for working on this great project.

DR. BATEMAN: Thank you.

We'll now circle back to the speakers who weren't present initially.

Speaker number 1, are you now available?

(No response.)

DR. BATEMAN: Okay.

Speaker number 6?

DR. DAVIDOFF: Yes.

DR. BATEMAN: Okay. Speaker number 6, please unmute and turn on your webcam. Will speaker number 6 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have five minutes.

DR. DAVIDOFF: Yes. Hi. Apologies for the lag beforehand. My name is Scott Davidoff. I also have no financial relationship with the sponsor. I was a primary investigator for the study. I'm a board certified pain management physician working at Main Line Spine, which is located in the Philadelphia area. I've been in practice for roughly 15 years, with a specialization in non-surgical pain management, specifically

specializing in back pain. I'm double board certified with the American Board of Physical Medicine and Rehabilitation, as well as the American Board of Pain Medicine. I'm also the Past-President of the American Board of Pain Medicine and remain actively involved in this board.

One of the most common presentations I see in patients is radiculopathy or lower extremity pain resulting from a lumbar disc herniation. I've seen upwards of 30 to 40 patients a week with this specific diagnosis. A lumbar disc herniation causing nerve pain in the leg can have severe impact in a patient's quality of life, as you've all heard from patient testimonies this afternoon. This includes decreased activities of daily living, decreased sleep, significant missed time from work, sometimes resulting in permanent disability. Patients often require multiple visits to urgent care or the emergency room, as well as primary care visits and other specialists before seeing a pain management specialist like myself.

In my practice, and specifically in our field of pain medicine, we use a variety of treatment options to manage this type of pain. This includes months of physical therapy or chiropractic therapy, both opiate and non-opiate prescription pain medications, and a variety of interventional procedures, most commonly epidural steroid injections. Oftentimes, 2-3 injections are needed per episode. Sometimes they're effective; oftentimes short term effectiveness. There are also patients that eventually require surgical consults and something called a spinal cord stimulator, which is a procedure which requires the insertion of a wire in the spine in order to reduce or eliminating nerve pain.

As stated before, when patients do not respond to these conservative care measures, they often require surgical evaluations and treatments. Surgical options include either a laminectomy or discectomy, or sometimes a lumbar fusion, which involves the insertion of metal rods in the spine. These surgical procedures carry significant risk

factors, including bleeding, infection, nerve damage, and sometimes increased pain afterwards. There is also an inherent risk of additional deterioration at the level of surgery, both at the level and/or above or below the levels after the surgery. Additionally, as you all know, all of these treatments, including surgery, carry significant healthcare costs.

During my time as the primary investigator in this clinical trial, I observed a significant improvement in both pain levels and quality of life in the patients enrolled in this trial. This includes a reduction in pain medication, as well as reduced physical therapy and epidural steroid injection requirements. Specifically, there was one patient that was able to return to running marathons several months after the injection. In a separate patient that was a full-time yoga instructor, she was on full-time leave, and within 6 weeks, she was back to teaching full time.

By decreasing the size of the disc herniation, thus resulting in decreased compression

of the nerve causing leg pain, this procedure can have a massive impact in the treatment of our patients. I foresee a significant decrease in the need for additional interventional procedures, medication requirements, physical therapy, and the reduction in the need for surgery. This will clearly have significant beneficial impacts on the cost of healthcare as well.

From a patient standpoint, along with avoiding the need for these above treatments, the impact will be seen significantly on decreased pain, improved function, and increased quality of life. I wouldn't hesitate to use the term "game changer" if this product becomes available to our field medication. I appreciate you all allowing me the time to speak this afternoon. Thank you very much.

Clarifying Questions (continued)

DR. BATEMAN: Thank you.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. We're going to

spend the next 20 minutes or so doing additional clarifying questions for the sponsor.

When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you, and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

I think there are some additional data from this morning that was requested that the sponsor is going to present, and then we'll entertain additional questions.

DR. STAUFFER: Thank you, Dr. Bateman.

We were asked this morning to provide you with some data on two elements. One was on patients with nerve root impingement, and I think that was a question, and then a little bit about patients with back pain and how did they do later

on. So, I'll first have Ben Vaughn speak to the nerve root impingement, and then I'll speak to the other elements of back pain.

MR. VAUGHN: Ben Vaughn, statistics. First, just a little context; again, this is 1131, our failed trial. I didn't do a great job of articulating the combination of these various factors, so we have a Venn diagram here showing you the counts in each; and that's really washed out, some of those numbers, but the bold numbers are the ones that we're really focused on.

The bold numbers add up to the subjects with clear nerve root impingement, and then you can see those slices on either side for no chronic lower back pain or no recent concomitant opioid use. For example, among those with clear nerve root impingement, we have 46 that didn't have chronic lower back pain, and then ideal subjects in each, we have 20 on active and 5 in sham. And you can see, we really do get into some very low numbers over on sham; so context for what we have there.

Then for the actual plot over time, this is

parallel to the FDA plots in that LS mean change from baseline. So you can see those tighter error bars like you saw in Study 1031 and Study 1133, the FDA plots. This is more parallel to what they did versus that plot that was just raw values. I hope that addresses your concern, Dr. Reich.

You can see that, consistently, we do have the subjects with clear impingement are falling lower. This doesn't look great. It's not wide separation. It's not the perfect picture. This study had many flaws. Those do include subjects that have some of these other covariates that could be increasing the variability or making it difficult to see separation, but we do have a very consistent picture of the ones with nerve root impingement falling lower and improving a bit more. And most importantly, when we corrected these things, when we add these to our inclusion/exclusion criteria, in Study 1133, we had a positive study. So once we aligned the populations to what we saw in Study 1031, it was a positive outcome.

DR. BATEMAN: So, I'm a little confused by the numbers. The number of patients in 1131 that had MRI-confirmed nerve root impingement was 69, I think, in the table we saw.

MR. VAUGHN: I believe it's 79 from the Venn diagram; yes, 79.

DR. BATEMAN: And some of the patients received treatment and some did not; right?

MR. VAUGHN: Those are the ones on active.

DR. BATEMAN: Okay.

MR. VAUGHN: So we have 79 on active and 21 in the sham group. Now, in that plot, we are just showing all the sham because method of action doesn't really matter for the sham.

Here are the Ns again.

DR. BATEMAN: Although the natural history could be different in those that have nerve root impingement than others. So is it possible to see just the clean group of those with MRI-confirmed nerve root impingement stratified by treatment versus sham?

MR. VAUGHN: We have not broken that out in

that plot. We just grouped them because, again, getting into those 21 subjects is just wildly noisy. And here's that plot again.

DR. BATEMAN: I just think the proposed label is adding this component with nerve root impingement, so that would be the cleanest representation of what is being proposed in the label. And if we have this negative study, 1131, that's different from 1133, I think it would be helpful to see those raw data for the population that the medication's being labeled for.

MR. VAUGHN: Sure.

DR. BATEMAN: Even if it is noisy, even if the confidence intervals are wide, it would at least give us a sense of is that a reasonable explanation for the differing results in 1131 versus 1133.

MR. VAUGHN: Understood.

I'm going to quickly turn it back to Dr. Stauffer to address the question about back pain.

DR. STAUFFER: Thank you. So as just a

general discussion this morning -- sorry, here's the slide -- this looks very similar to what you might have seen in the core deck. We just wanted to put the story together for you side by side, both trials at 13 weeks, to give you a sense, and the general sense, of the overall impression of this drug, not only the pain scores for the most important thing, which is the leg pain, but also did it make back pain worse.

I think the FDA pointed out that the point estimates still favored the drug in both of these trials, not only at 13 weeks. And not only is pain important here, but also other elements for these patients. I think you heard patients talk about their functional improvements, and we have some responder analyses that are here as well, and quality-of-life assessments, too.

So, this is all very consistent with the clinical meaningfulness of the drug and what it can do, and that's not only true at 13 weeks. And you can see what I'm showing you here, but I'll show you the same look at 52 weeks. So, this is out to

a year, the same idea. Again, we just want to make sure we addressed your questions on low back pain. Thank you. You guys don't have copies of that. If you'd like those two slides, we have those copies here for you, if you would like them later.

DR. BATEMAN: Okay.

Dr. Schiff?

DR. SCHIFF: Yes. Thank you. One quick question is, in all of the 29,000 patients who've received these injections, I'm old enough to remember chymopapain. Did anyone get a known subarachnoid injection? Anyone can answer.

DR. MARTIRE: Diane Martire, safety. There are no reports in the postmarking safety database of injection into the subarachnoid space.

DR. SCHIFF: Thank you.

A harder question for the group is, if I look at the inclusion and exclusion criteria for the last clinical trial that was positive, they seem extensive and superb. They're all the reasons that you might get discouraged at surgery for lumbar back pain and leg pain from herniated discs.

And maybe if our surgical specialists used such criteria, our outcomes on the few patients that we would operate on would have been much better.

When I look at the 1131 study, those criteria were much less restrictive. We think that's the reason for the failure against sham. But in practice, if approved, I think there's a risk that the entrance criteria effectively applied is going to be less restrictive as the clinical trial, and that there's a risk that the outcomes could look very much like the failed clinical trial.

I'd love to hear comments on how the extremely restrictive criteria, which I think were very good, for the last clinical trial would translate into practical use for an approved compound. That's the hard question for whoever wants to address it. Thank you.

DR. STAUFFER: Thank you. I'm going to have Dr. Kim address your question as a neurosurgeon.

DR. KIM: Kee Kim, neurosurgery. Everyone that comes into my clinic is slightly different.

When I look at the patient and examine the patient and get the history, and have an MRI that is showing herniated disc that's causing their miserable pain, I want to know what they've tried, of course, and that's part of the process. If I feel like they've tried adequate stuff, then surgery will be brought up.

Now, if condoliase is available as a treatment, of course, that would be a discussion I would have. And I feel personally, based on the data that I have, and I was also part of the study, that this will be something that I would recommend to my patients to try first. And I'll tell my patient, "You're not going to burn any bridges. If this doesn't work, I'll go ahead and operate on you."

DR. SCHIFF: Thank you.

Let me ask this question slightly differently. If this were approved, based on the last clinical trial, you'd have a package insert that would go on for page after page of inclusion and exclusion criteria, and I don't think that's

going to happen. How do you translate why that trial showed significant improvement into practical usage, assuming that most practitioners aren't as good as Dr. Kim?

DR. STAUFFER: Joe Stauffer, advisor to SKK. This drug is for the pain practitioner, ideally, first-line treatment for the pain practitioner after patients have suffered through; and all the clinical trials need to be discussed as best we can in the clinical package insert, of course. The marketing materials and medical education materials will also bear some of that as well.

We fully expect that physicians who use this understand how to use it. They select for the right patients. It will not work for everybody, and we acknowledge that; and there are certain patients that it may work for and then not work down the road. We acknowledge that as well, as Dr. Kim pointed out.

But we believe that we've got a solid drug here. There's a radiologically visible nerve root impingement, and that's the patient that's to be

selected. These are folks who have suffered at least 6 weeks or longer. These are also folks that they're unresponsive to other therapies. It fits with the mechanism of action of this drug, proven both preclinically and clinically, so we believe that that would be the best way to describe that in the package insert. We'll work with the agency to do that, of course, and then to use that in the marketing medical education materials as well.

DR. SCHIFF: Thanks.

DR. STAUFFER: You're welcome.

DR. BATEMAN: Dr. Schiff asked questions about efficacy. I just want to follow that up with a question about safety.

DR. STAUFFER: Yes?

DR. BATEMAN: In the postmarketing surveillance data, there were 5 cases of severe cutaneous adverse reactions, life-threatening cutaneous adverse reactions. I wonder if you could just speak to the way those cases were ascertained. If you look at the rate of these SCARs, it's approximately 1 in 5,000, quite a high rate for

such a serious complication, and if you could just reflect on that.

DR. STAUFFER: I'll have Dr. Martire address your question.

DR. MARTIRE: Diane Martire. I'll start with the AGEP, the acute generalized exanthematous pustulosis cases. One of these was solicited from the ongoing survey and another one was spontaneous. What happened was these patients presented with a rash 2 days after injection that became pruritic. They sought medical treatment. They developed the pustules. It was recognized by a dermatologist as potentially related to drug. They were treated with topical steroids and antihistamines. Two of them had a skin biopsy which was consistent with AGEP, and they followed the typical clinical course of AGEP, which is resolution within 2 weeks with some desquamation. So, we believe that those are real cases of AGEP as determined by skin biopsy and clinical course.

Regarding the case of erythema multiforme, it was a mild case presented with a maculopapular

rash within 2 days of injection of condoliase. They did not develop mucosal erosions, systemic symptoms, or skin detachment, which would be the hallmark of a more severe SCAR. They were treated with steroids and antihistamines, and they eventually resolved.

The SJS case, the diagnosis was then revised to anaphylaxis because the initial reporting doctor reported it as -- a lot of these represent maculopapular rashes, which in the clinical world are very confusing and cover a range of symptomatology. This patient developed a rash, and the next day had urticaria, a little bit of scratchiness in the throat, so it was determined that was actually more consistent with anaphylaxis because they did not go on to have a blistering skin rash, skin detachment, and mucosal involvement, which were the hallmarks of SJS. So, fortunately, that patient also resolved.

DR. BATEMAN: Then, can you just speak to the degree to which these cases are being captured comprehensively in the postmarketing surveillance?

Are are you relying on spontaneous reports or was there systematic surveillance?

DR. MARTIRE: So, there's an ongoing survey in Japan postmarketing. As I mentioned, that's where the solicited cases come from, and there's reporting that goes on there; otherwise, it's the routine pharmacovigilance that's ongoing in Japan, which is spontaneous reporting.

DR. BATEMAN: And how many patients were surveyed or how many practitioners?

DR. MARTIRE: Currently, there are -- it's in one of your briefing documents -- about 4,000 patients that have been involved in this survey in Japan. That study's still ongoing. The report will be available next year.

DR. BATEMAN: Dr. Nelson?

DR. NELSON: Ariana Nelson. This is a question for possibly Dr. Martire or possibly Ben Vaughn. I'm just curious how you decided on the dosing for Study 1021 because it seems that you adopted the lowest dose. So I'm unclear when we decided that that was the lowest effective dose, if

you could comment on that.

DR. STAUFFER: I'm actually neither Dr. Martire or Dr. Vaughn., but I think I can address this question for you. Joe Stauffer. Sorry; I've got to get closer to the microphone.

Study 1021 was the dose-range finding study. It was four treatment arms: low, medium, and high dose, so a 1.25 middle dose, and then a higher dose at 5 units. There was a placebo arm as well. It was pretty much a flat dose-response curve, so there was no real difference between the 3 doses for the drug; however, there were some more adverse events in the higher doses, the two higher doses, and that's how the drug was picked. It's harder to make this drug at a lower concentration than the 1.25, just for manufacturing purposes and for consistency, so that's how the dose was selected.

DR. NELSON: Thank you.

DR. BATEMAN: Dr. Reich?

DR. REICH: Yes. Thanks. I have a few, some in preclinical, then some statistical. I wanted to return back to that 1131 failed data, and

then some safety questions, if I can.

DR. BATEMAN: Okay. We don't have a huge amount of time.

DR. REICH: Okay. On the preclinical side -- I'll just ask, and then you can respond, and I'll rifle through them -- any proteolytic activity in vitro that was characterized or not? Enzymes are very pH dependent, and I'm assuming that the pH of the nucleus pulposus is physiologic, around 7, but do we know that's the case in herniated discs? What about diffusibility and elimination? How is this enzyme actually eliminated?

DR. STAUFFER: So, a lot packed into your question there. I'm going to have Dr. Spehalski address your question.

DR. SPEHALSKI: Hi. Liz Spehalski, nonclinical. The first question was proteolytic activity. I can show you that condoliase has very specific activity for chondroitin sulfate. We don't see any proteolytic activity of it. It's very specific for chondroitin sulfate with some

minor activity on hyaluronic acid. Additionally, I have data here that I can show you regarding just looking at casein and bovine serum albumin, two proteins, that condoliase does not show activity over water.

The second question, pH. The pH of a disc, to my knowledge, is the same as the physiologic pH, but I'd actually have to double check for you. Then, the last question was about PK, metabolism.

DR. REICH: Yes, diffusibility and elimination.

DR. SPEHALSKI: Sure. We have data nonclinically that suggest that condoliase stays at the disc in animals, and monkeys, and dogs for about 30 days. It's not detectable at 90 days by ELISA. We don't see metabolism at the disc itself. It's whole condoliase, so what we see is that it's gradually eliminated at very low levels, undetectable levels, into the plasma, where it's metabolized just like a protein would be, eliminated like a protein.

DR. REICH: Okay. In terms of the trial and

interrogating the data, can you comment on PT rehab, which was allowed to continue, and how balanced that was over the course of the study? And also with respect to rescue meds, how balanced was that over the course of the study?

DR. STAUFFER: So, rescue meds, I can do that first because I know we have that as a backup slide; if I could have that, please. They're pretty balanced, by the way, in the rescue medication throughout all these trials. There was no significance between one or the other, be it be it opioid, or NSAID, or Tylenol. That I do know, and if I have the slide up, I can show you, but it was generally balanced.

In terms of physical therapy, I think your question is, did patients have more physical therapy or less? They were stabilized on their physical therapy. They weren't allowed to increase or decrease as part of the trial, and that was part of the enrollment criteria.

DR. REICH: And balanced as well?

DR. STAUFFER: That I'd have to get for you.

Sorry. I don't have the PT.

DR. REICH: Sure. That's excellent.

Maybe a question for Ben Vaughn. In terms of the variance between the modified intent and the actual intent to treat, the numbers are not large, but I'm just wondering how that was defined.

MR. VAUGHN: I do not know off the top of my head. It was only one or two subjects that were eliminated. I think it was they had to actually be treated for the modified intent to treat, so there were two subjects that, for whatever reason, were not injected, but a very small number.

DR. REICH: Got it.

On the MRI findings, you talked about the volume of this, but did it actually look by that metric of impingement and whether there was MRI resolution of the impingement?

DR. FUERST: Tom Fuerst, radiology advisor. That's a good question. We did not look after screening at any changes in the impingement status. We did look only at the volume change. We relied on the efficacy endpoint of pain.

DR. REICH: Got it.

I wanted to go back to 1131, and maybe flesh out more of what Dr. Bateman was struggling with. In the FDA book, table 4, again, I could be misreading this, but it looks like -- I don't know if you have that -- you have it broken down by what Dr. Bateman was looking at, which was the MRI-confirmed nerve root, whether it was present or not in the treatment, in the patients who received treatment, and then broken out by the other factors: back pain, chronic comorbidities, and spinal comorbidities.

Is that gettable?

MR. VAUGHN: Am I recalling correctly -- you have it right there; we should look at that. I think it's negative 40 versus negative 36.

DR. REICH: Correct.

MR. VAUGHN: Yes. That's consistent with what we've been saying. That is just in the active group, but what that's showing is that there was a 40-point improvement in the subjects with visible nerve root impingement versus a 36-point

improvement in active subjects without the nerve root impingement.

DR. REICH: Yes. Again, when I look at this, what strikes me as driving the failure of the study is the back pain, the chronic pain comorbidities and the spinal comorbidities, that seems to be driving the larger variance a little bit to the MRI, plus or minus the impingement. Then, on table 7, you also had a big imbalance in terms of history of muscular skeletal disease and past psychiatric history.

So, I'm just wondering why we didn't put more emphasis on these imbalances. And don't get me wrong -- and I'll get to this later in the comments period -- that I like where you landed in terms of screening and enrolling people only with MRI-proven impingement. But again, just looking at the data, I'm wondering why that was so prominent.

MR. VAUGHN: So, this was done at the time that we had our first Japanese study and our first U.S. study, so it was what the sponsor identified at that time as being the most clear issues with

the trial. With the nerve root impingement, it's very obvious. There's a valid clinical reason why this would have that impact, so that really jumps out, and it was a clear failure of that trial, being that we only had 27 percent of the subjects with that nerve root impingement.

With some of these other things, these are items the agency looked at, and I think their conclusion was that you couldn't get to a clear conclusion; that these things may have impacted it, it may have not; however, we do have one thing that we know has this very clear clinical validity, and it does seem to pop out a bit.

I will point out, again -- I know I keep harping on this -- these last two items, 18 and 9, it's just very hard to draw conclusions once you get into these small Ns, and it's not randomized; it's just what popped out in the data, so no alpha control. It's just difficult to really get to something when you don't have that clinical link as well, where you know this is how the drug works.

DR. BATEMAN: These are just the changes in

the treatment arm. These are not --

MR. VAUGHN: Yes, this is active arm. It's not subtracted.

DR. BATEMAN: So we don't know the other side.

DR. REICH: Got it

MR. VAUGHN: Correct.

DR. REICH: Just a few more. Thank you.

DR. BATEMAN: How about one more?

DR. REICH: Okay.

On the safety side, I looked at Xiaflex, that collagenase may be a decent proxy as a biologic that's also an enzyme. Can you refer to the safety profile of a commercially available injectable enzyme to help us put the safety profile of this in context?

DR. STAUFFER: We don't have any specific data on other compounds. Specifically what you're asking for -- I think you said Xiaflex -- we don't have any specific data on what that might look like.

DR. BATEMAN: Okay. We are now going to

proceed with the charge to the committee from Dr. Doshi.

Charge to the Committee - Tina Doshi

DR. DOSHI: Thank you, all, for your attention and thoughtful consideration of the issues thus far. As I mentioned in my introductory comments, we are now asking you to consider several key issues. You should be able to see our questions on your screen shortly. Since they're going to be read verbatim for the public record in a little bit, I'm just going to paraphrase them now to put them into context.

We have five discussion questions and one voting question for you to consider. First, we'd like for you to discuss the impact of the negative study, Study 1131, on your assessment of the population with the best benefit-risk relationship for this product and how that information from the study should be conveyed to prescribers who might be considering this drug for their patients.

We've also described two categories of safety concerns: spine-related adverse events and

immune-related adverse reactions, including hypersensitivity and severe cutaneous adverse reactions. We will be asking you to comment on the significance of those. Common to both efficacy and safety, we would like to hear your thoughts about assuring appropriate patient selection and patient safety with regard to the appropriate requirements for proceduralists and setting of administration. Lastly, bearing these discussions in mind, we'll ask you to vote on whether the benefits of condoliase outweigh the risks, and to provide a rationale for your vote.

With that, I'd like to point out that on the agenda, there's a small error. Dr. Bateman will be guiding the discussion and the questions. So with that, I'll turn it over to Dr. Bateman, and I look forward to the committee's discussion.

DR. BATEMAN: Thank you.

We're actually going to take a 10-minute break, and then we're going to resume with our deliberation on the the questions, and we'll just go straight through until the end. So a 10-minute

break, and we'll be back at 2:32.

(Whereupon, at 2:22 p.m., a recess was taken, and meeting resumed at 2:32 p.m.)

Questions to the Committee and Discussion

DR. BATEMAN: The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with questions to the committee and panel discussions. I would like to remind the public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording.

We'll proceed with our first question, which is a discussion question. The question is, comment on the significance of Study 1131, the negative study, in the context of the other two positive studies with respect to establishing the efficacy of condoliase.

Any questions regarding the wording of the question?

(No response.)

DR. BATEMAN: If there are no questions or comments regarding the wording of the question, we'll proceed with an open discussion of the question. Please, again, indicate that you'd like to speak by turning your name tag.

Dr. Schiff?

DR. SCHIFF: I'm fascinated by the different sandwiching of the two positive studies. The indications were quite different. Why the first positive study in Japan had such good results, it contains information that we just don't fully understand. It's a very homogeneous population. One of the things I do is I also look at population-level genomics, and it was a different group of people, heavy laborers, fairly young, not as overweight as the U.S. population, but they didn't have the confirmed image-guided mechanism that we anticipate the compound addresses, and then the two U.S. studies, a very different population.

I think in retrospect, I'm not surprised at the failure, but as I mentioned briefly before, how do you translate the success of the second study, given what I also feel is a very rigorous inclusion and exclusion set of criteria? How that gets translated into approval without having our results then turn into a lot of people with back pain are getting injected, and having the outcome look like the failed study, is my concern. I wish I had a better answer, though, to those differences.

DR. STAUFFER: It mentioned the Japanese study did not have confirmed nerve root impingement. I believe the slide that is up -- hopefully will come up -- will address some of your questions or some of your commentary.

DR. BATEMAN: We're going to try to keep focused on the discussion for now, and we'll ask you for additional clarification if we need it.

Dr. Bicket?

DR. BICKET: Thank you.

Dr. Schiff, I appreciate your comments, and just one comment there from Dr. Sudhakaran's

presentation. While the Japanese study didn't confirm as an eligibility criteria that people have nerve root impingement, it seemed from data he presented, that about 80 percent of those patients did have nerve root impingement there, which I think pushes us back to that discussion about that being a key factor on the indication.

When I think about this 1131 study, a part of it is a question of parsing out what can we take away from that negative study and to what degree does it need to modify that label? I do feel with these two positive studies, from the information that's been presented both by the sponsor and by the FDA, and reading the studies, that they're meeting that mark of saying, "Look, we do have significant efficacy that's there." I have gone back and forth about this idea of, well, does there need to be further restriction besides just saying we need MRI-guided confirmation of that nerve root impingement?

I do know that, for context, if I'm just thinking more globally, 1131 I believe was

conducted between 2013 and 2017. It's a time in the United States where we're seeing still prevalent but somewhat declining rates of opiate prescribing in the general population. We know that people were prescribing opioids for low back pain quite commonly. It's not to say that that's totally gone out of favor, but I do believe that there have been efforts that weigh in here about thinking in the future years that the use of opioids is going to be less prevalent, though it will still happen for some patients; and that tempers a little bit of my concern about the influence of opioids and not necessarily needing to declare that someone needs to be opioid free to receive a treatment like this were it to be approved. Those would be at least some of my initial thoughts about how the study fits in between the two. Thank you.

DR. BATEMAN: Okay.

We'll go to Dr. Kennedy next.

DR. KENNEDY: Thank you. Specifically regarding the positive studies and negative

studies, I think this represents a natural evolution in study design, and I don't have a real problem with it, especially because of the US-based nature and different patient populations. Your first study, you find negative, and then you do subset, you do a cleaner study the second time, and I don't have a problem with that, but I do think that affects potential labeling.

I will agree with the comment just made about opioids decreasing. It's really a strong covariate, but I think in addition to the specifics of nerve root impingement, back pain equal to or greater than leg pain changes things a lot. The notion that if you decrease someone's leg pain and they have equal back pain also, they're 50 percent better is probably not accurate. They're still on the same degree of pain is what I find.

We know that practice patterns -- we heard from a number of testimonials of really strong effect, which was really impressive, but you also heard them almost ubiquitously say, "Yes, we were offered surgery right away." So when broadly

applied, the application will probably be much more similar to the negative study unless there are significant efforts to make that not the case.

DR. BATEMAN: Thank you.

Mr. O'Brien?

MR. O'BRIEN: Sort of echoing the others, when I look at the significance of 1131, it's from two different perspectives. From the perspective of providing the data of efficacy and safety, what the FDA has said and whatever, I think the combine positive studies should give one appropriate approval rating.

On the other hand, I fear that 1131 is really an omen of things to come. We've seen so often when something gets approved, that all of a sudden it's off label and it's given. I think 1131 tells us, hey, there's a huge population out there of individuals that are in this situation where they're going to want to have that, and I think it's going to be applied. And it may be just telling us that we're going to have a large group coming up in the years ahead once this thing is

approved and out there, from a practical thing.

So I guess it does come back to me in terms of making very sure that the label and the indications are very specific on this patient population, and go beyond -- I think there has to be more that's eked out of those 4 pages of excludability that was on the subsequent study that has to be pulled into that label and be very specific, because I think we're creating a tidal wave.

DR. BATEMAN: Dr. Kirkpatrick?

DR. KIRKPATRICK: I put my sign down because it's been discussed. Thank you.

DR. BATEMAN: Dr. Reich?

DR. REICH: Yes. Thanks. Jeff Reich. Just to respond to Dr. Schiff, I'll echo what Dr. Kennedy was saying. I like the term "evolution of study design" because I think that's exactly what we've seen and should be commended. Clinical trials, at best, are artifacts. Closely, you try to approximate what goes on in the real world, and clinicians hopefully are able to translate that.

So, inclusion/ exclusion criteria, for example, are always a necessary condition of a clinical trial and never reflect what goes on in clinical practice.

My interpretation of 1131, as I said before, was focusing more on the fact that a lot of these people had other sources of their pain, and I think that's really driving the discordance, and it makes perfect sense. People with other mechanisms of their pain, people with chronic pain and maybe have an element of central sensitization, et cetera, are not going to respond to this very, very specific targeted therapy.

Despite all that, I like that they landed with a label that calls out discrete impingement because when I first looked at this, and putting on my neurology hat -- which by the way is generally the front line of this condition. It's usually the neurologist that screens out all these patients initially, and then refers them on to interventionalists.

My first concern was we're going to get an

intervention for a lot of people with diffuse nonspecific back pain with disc bulging because that's exactly what you see, and I think that would be a pendulum that swings too far the other way. But being able to specifically call out radicular pain, being able to really correlate that to MRI findings of discrete impingement makes clinical biological sense.

DR. BATEMAN: I would just add to that. I am a bit skeptical that what's driving the negative results in 1131 is the MRI-confirmed nerve root impingement versus not. If you look at the change in VAS stratified by that factor, and we saw table 4 from the FDA's briefing packet, the change in VAS is basically the same in the two groups. There are a whole host of factors that were narrowed in 1133 that may account for the difference in results, but I think it's more than just the MRI findings.

Other comments? Mr. O'Brien?

MR. O'BRIEN: Well, I guess my only comment that generated to me, specifically, is that. I

think, from my perspective, I represent spine deformity patients. So if we're altering the vertebra, I'm concerned that that population is going to be getting this. And now we have the mechanism of mechanical difference that's going to occur in the spine, and we're going to have a lot of people that are actually worse than they were before. So that's a population that I'm concerned about.

DR. BATEMAN: Okay. Any other comments regarding question 1?

(No response.)

DR. BATEMAN: Okay. I think the committee pointed to a number of factors that could account for the difference between the two positive and the negative study, 1131. The differences in patient population in the initial Japanese trial, the patients tend to be young, not overweight, often physical laborers.

Moving on to 1133, the trial had quite narrow inclusion criteria that were quite different from 1131. That might account for the observed

difference. I think there was a feeling amongst the committee that if you can isolate MRI-confirmed nerve impingement and clear sciatic pain, that's differentiated from chronic lower back pain or pain for which opioids have been chronically prescribed, that is a biologically plausible explanation for the difference that's observed. But I think there was also concerned voice that the population in the negative study might reflect the population that the drug would ultimately be used in more than what was observed in the trials that were successful.

Is that a fair summary? Any additional comments to add to that?

(No response.)

DR. BATEMAN: Okay. So we'll move on to question number 2. Question 2, discuss what concepts might be included in the prescribing information to help clinicians identify patients who would have a favorable benefit-risk profile if treated with condoliase. The applicant's proposed indication states that condoliase is indicated for the treatment of radicular leg pain associated with

confirmed nerve root impingement caused by lumbar disc herniation in adults. Does this indication reflect the most appropriate patient population for condoliase, and if not, what modifications could be made?

We'll start with Milan.

DR. STOJANOVIC: So, to echo what was discussed just recently, even with narrowing indication in the last study, 33, we have a good response and good results that's significant but not amazing. So if you look at the categorical data, you have 30-50 percent patients that improved. That's a relative narrow margin between placebo or sham, or treatment, but still significant, and it's good. We heard the patients said are good things.

It is good things, but if this is overused, and if it goes out and starts being overused, we're going to go back, even to maybe worse results and start at 31. We've seen this happening, and that can be bad long term for patients. Insurance companies might not approve it, and it might be bad

for everyone, so I think we have to control this.

The same with impact guidance. I agree with impact guidance in a sense. Yes, 10 or 1 of NRS is significant, but most studies look at the minimally important change, at least 2 of NRS, or 30 percent, 50 percent. So we have good results, but we have to narrow the inclusion criteria. I agree that impingement of nerve root is a good thing to stick with.

We have to clearly convey this so insurance companies can pick that up, too, and restrict from predictions to getting open and doing for everything. Some suggestion is maybe to do a better grading of the MRI compression. There are all kinds of things: anatomical, location of this protrusion, and severity of this protrusion that is contacting the nerve root, as we said, nerve impingement.

As I mentioned before, complete radial tear, that you have a tear and leakage of this material, this indication, there should be contraindication maybe. And if you consider maybe leak or a

questionable small tear, how about the fact a lot of people have initial pain? That terrible pain is because of the chemical sensitization. So should these people have ESI first before going to this treatment? Should this be a necessity to try epidural first before getting approved?

We talk about the age. The older age people don't do well, but I wouldn't discriminate with age. We know that this degeneration is bad with age, but some people, for whatever reason, genetic or how they take care of themselves, they have great discs still at the advanced age. So maybe age of a disc would be something to look at in the future.

Then I think it has to be clarified it is not approved for cervical radicular pain. I know this is assumed, is untitled, but it should be clarified for thoracic because out in the practice, why not trying for this before we see the studies? That's what I have to say.

DR. BATEMAN: Thank you.

Dr. Sprintz?

DR. SPRINTZ: Thank you. Dr. Michael Sprintz. I appreciate what was shared in terms of both the safety and the efficacy. The two things, A -- and I'm echoing some of the things that have already been talked about -- I'm in agreement that we need more clear indications of appropriate patients, and I think the wording should definitely include those who have failed conservative treatment.

I think there is value here on a couple parts. If we can delay surgery -- and, grant it, the evidence doesn't show, well, we totally prevent it, but the fact that you can delay it is good. When I start to think about patients who fail conservative therapy, I think differentiating between something like ESIs versus NSAIDs would be significant because I can see, in clinical practice, someone's going to go, "Oh, well, have you tried ibuprofen?" "Yeah, and it didn't work." "Okay. Well, you failed conservative therapy, so we're going to move straight to this," versus someone who's like, "Yeah, I've done two ESIs. I

got a little bit of relief, and then none at all." That's a totally different patient.

So, I think clarifying what we talked about, I think you do need to have statements about having failed conservative therapy, but I think how we define that needs to be a little bit better to prevent people from going, "Oh yeah, so you tried some over-the-counter stuff, and that's conservative therapy; therefore, we can move forward based off of the indications."

So, that's the one piece, but I also see value in the fact of what do you do for those patients who may not want to do surgery or who are moving towards that if you can prevent it; and they're like, "Well, Doc, what are you going to give me in the interim?" And inevitably, it tends to be opioids. Even though it has decreased over the years, we still see that.

So, this is another option that's a non-opioid intervention that could potentially be beneficial for those who have failed, I would say, more interventional conservative therapy like ESIs.

So I definitely do see value, but I think we need to include failure of conservative therapy, and I think we also need to better define that. Thank you.

DR. BATEMAN: Thank you.

Dr. Kirkpatrick?

DR. KIRKPATRICK: Thanks. Most of what I was going to say has been said, but I'll add. Fundamentally, the indications for this are the same as doing a laminotomy for discectomy. They've got to fail their non-operative care. They have to have a concordant imaging to a specific dermatome and myotomal radiculopathy that correlates. Those are the key things that I think that the FDA team can make sure that we try and incorporate. Thank you.

DR. BATEMAN: Thank you.

Dr. McAuliffe?

DR. McAULIFFE: Maura McAuliffe, East Carolina University. We're talking about the benefit-risk profile. I'm interested in women's health, and there are two groups of patients we

haven't talked about at all that may have long-term risks associated with this, one being those with osteoporosis and those taking bone-modifying drugs, the bisphosphonates. I don't know whether there's any postmarketing data including that group of patients, but it would be interesting to know for labeling purposes.

Also, the women, what advice are we giving them about becoming pregnant? I know they were excluded if they were pregnant, but right about the time that the third trimester hits, we have the largest decrease in disc height of 15 percent. So those together could set up somebody for some spinal instability.

DR. BATEMAN: Thank you.

Dr. McCann?

DR. McCANN: Mary Ellen McCann. I just have a question of the group because I think a lot of you know more about laminectomies and epidural injections. I had to quickly look up what ESI was.

DR. SPRINTZ: Sorry.

DR. McCANN: No, that's okay. But after you

have an ESI, is there a time frame before you can go on to your laminectomy, or can you have an ESI and then the next day get a laminectomy? And if that's the case, do we need to worry about the ESIs with these injections?

DR. KIRKPATRICK: So, my neurosurgical colleagues can also chime in, but in my opinion -- and it's an opinion thing; we don't have research studies to show how soon after epidural block, for example, or ESI, what are the complications related to doing surgery shortly versus long -- most of us would give it at least 6 weeks to see if an ESI helps at all. But that also combines with the natural history because the longer you wait, the better they taper.

DR. McCANN: Right.

DR. KIRKPATRICK: I don't think the placement of an epidural steroid injection complicates my surgery other than potentially a small risk of infection because of the steroid reducing the immune response.

DR. McCANN: Right. So I would imagine the

same considerations would apply to injecting a substance; right? If you give steroids, you have decreased inflammation, more risk for infection, and then you put another foreign body in.

DR. KIRKPATRICK: I think we're going beyond the scope of what we can consider here because they obviously didn't study it. But this is a chemical, and it doesn't have immune-modifying properties, as far as we can tell, like a steroid would.

DR. McCANN: Right.

DR. KIRKPATRICK: So is it like having another device in there? I don't think it's really a device; it's a chemical. It might make it a little bit different in that if you did this, and then went in within a week, you may not see any difference, or you may find the pain goes away before you get them to the operating room.

DR. McCANN: Yes. My concern was, basically, not that that's what this committee is supposed to do, but advocate for aggressive conservative therapy, and should there be a timeline with that.

DR. KIRKPATRICK: And I agree that a timeline would be a good thing to think about.

DR. BATEMAN: Okay. Thank you.

Dr. Schiff?

DR. SCHIFF: Yes. I very much like the way Dr. Kirkpatrick just summarized a lot of complexity. The indication should be the indication for properly selecting patients for open surgery, but I think there should be one qualification on that.

Some of the best surgical candidates have free fragments of discs, and those are the people we often get a fantastic surgical outcome with. That has to be qualified here because those are patients for whom this shouldn't help at all. And they also get into the realm of if there's a large enough hole in that annulus with missing material, you would anticipate you have the greatest risk of extruding the drug into places it shouldn't be.

DR. BATEMAN: Thank you.

Dr. Kennedy?

DR. KENNEDY: Yes. I agree with most of the

comments made thus far, really differentiating conservative care but challenging the label indication. I would add two things specific to this to mirror the results from the most efficacious study done in the U.S., which is, I would define the time frame of 6 weeks. I mean, that was designed. And at a minimum I would say, for those that do not have back pain greater than leg pain, I might actually argue that we would say -- in this criteria, because we're not recreating the very rigorous criteria of the study that was positive, we simply say that they have radicular leg pain greater than back pain, given that is a true indication of the medication.

DR. BATEMAN: Thank you.

Dr. Stojanovic?

DR. STOJANOVIC: Milan. Regarding infection, I agree there are some guidelines on that, too. We mentioned some patients who recalled they got a numbness. How about the numbness and weakness? A significant sensory deficit and weakness, from a surgical perspective, these

patients might need to have a surgery first or should that be indicated? That's something that might be important there.

DR. BATEMAN: Dr. Kirkpatrick?

DR. KIRKPATRICK: I'm sorry. I'm taking that as a give and take question. Patients that come with lumbar herniated discs that have a documented weakness are jumping in line. So, what we'd have to tell our patients is that the longer you wait on getting that strength back, the less likely it is to come back. So if we get the pressure off relatively early, then you have a better chance of recovery. Also, we're excluding from the whole discussion cauda equine syndrome, which is a large herniated disc that has incontinence associated with it and bilateral leg pain. That's off the table, in my mind; yes.

DR. BATEMAN: Dr. Reich?

DR. REICH: Yes, two comments and one suggestion. Just to echo Dr. Sprintz's view about somehow incorporating failure of conservative treatment makes just good medical sense, with the

paradox or conundrum there that ESIs have not met the same registrational level of scrutiny and approval that we are now considering; so I don't know how you suggest or allude to a treatment that hasn't itself met regulatory standards. That's one thing. In terms of adding to Dr. Kennedy's point about greater than back pain, I know the intent is good, but, to me, that just muddles it and invokes any back pain whatsoever, and I'd rather this be clear radicular pain, full stop.

The suggestion I have, and at the risk of sounding trivial and persnickety -- but that is generally what neurologists are accused of -- the leg technically is anything below the knee, so plenty of my patients with sciatica had pain just radiating into their buttock. So I wonder if it would be better to just say radicular pain and not make that -- I think it would be less confusing and more accurate than just confining it to leg pain.

DR. BATEMAN: Dr. Kirkpatrick?

DR. KIRKPATRICK: That's a great point, but that would emphasize that they need to keep the

indications that they used in the studies, which is L4-5 and L5-S1, and not think about L2-3 or 3-4, which do often stop above the knee.

DR. REICH: I agree with that, but S1-L5 radiculopathy often presents as buttock pain.

DR. KIRKPATRICK: Admitted. Typically, I don't operate on those if they're just buttock pain.

DR. REICH: Okay.

DR. KIRKPATRICK: That would take them out of the consideration of this because we're looking for leg pain.

DR. REICH: Fair enough.

DR. BATEMAN: Dr. Bicket?

DR. BICKET: Thanks. Just in follow-up to that, your point about this pain radiating to the buttock versus going down the leg, I think does make an interesting observation about how that pain is categorized and how people think of it. And maybe I just wasn't clear, and I'm not sure if there's the opportunity to hear from the sponsor about where pain that went to the buttock would

have been classified, based on leg pain versus buttock pain, but that could be, I think, informative to our discussion now.

DR. STOJANOVIC: I mean, clearly, radicular pain in corresponding dermatomal distribution of disc herniation. I think that clarifies it.

DR. BATEMAN: Dr. McCann?

DR. McCANN: No. Sorry.

DR. BATEMAN: Okay. Any other comments?

(No response.)

DR. BATEMAN: Okay. I think in summary, the committee felt that the benefit of the treatment is going to be achieved in the population for which it was shown to have benefit in the clinical trials, so it's going to most closely reflect the patient population that was treated and the inclusion criteria for trial 1133. The observation was made that closely matches the population that generally benefits from surgical procedures, with some caveats that if there are fragments of discs or really large defects, that it might not be an appropriate treatment in that context.

There was a strong feeling that the label should include that conservative measures failed, and that that should be defined with some specificity what those conservative measures are, and that there should be some notation of time course, and perhaps even some of the specific therapies that have been attempted and failed.

Any other key things to point out? Yes?

DR. SCHIFF: Yes. The issue of motor weakness and sensory deficit is important because those people are at high risk to delay for the reasons Dr. Kirkpatrick mentioned.

DR. BATEMAN: Okay. Fair enough.

We'll move on to question number 3 then.

Question 3, the data support that condoliase reduces radicular leg pain in a subset of patients; however, digestion of chondroitin sulfate in the nucleus pulposus subsequent to condoliase injections results in a decrease in disc height and modic changes. Given the known function of a healthy disc, reduction in disc height volume may result in disc-related complaints such as axial

back pain or might affect surgical options/ outcomes.

Discuss the clinical significance of these potential unintended consequences related to the mechanism of action of this product or whether additional data are needed to adequately assess this risk.

Hopefully, we'll hear from our surgical colleagues.

Dr. Kirkpatrick? Dr. Stojanovic?

DR. STOJANOVIC: We saw one slide showing that modic type 1 changes, numeric type 1 changes and to lesser degree, too, are similar after discectomy, 32 versus 25 percent. There's a meta-analysis just recently published, and there's another paper showing that, yes, after surgery, modic changes can occur, so surgeons might comment on this more.

I just want to comment that this is similar to surgery, and surgery would be alternative treatment to this, so that can be acceptable. The other thing we looked at is one year after

procedure, it might be that long-term modic changes can cause more pain.

In parallel to these last couple of years, there have been, really, lot of data supporting, actually, axial back pain and modic changes. As you probably heard, basivertebral nerve ablation is a new treatment. It's actually well supported by studies, and maybe one of the best MRI indications for treatment of axial back pain, and the evidence is pretty good.

So devil's advocate would say that maybe after years, this can develop into axial back pain, and when treating radicular pain, this can occur. The good part is that after surgery, this might happen as well, so I just think we need to follow the data along the way. This is something that has to be done in studies, but in a company, or if this gets approved, in some way. That's my comment.

DR. BATEMAN: Dr. Kirkpatrick?

DR. KIRKPATRICK: I've got a couple of things that I think fit best into this category or this question. One of them is, in the

understanding of my background in orthopedics and spine surgery, most of our major journals don't even think of reviewing articles if they don't have two years of clinical follow-up after an intervention. And this one is going one year, and then, obviously, you have thousands in the kitty, but they're not being studied. And the reason for that is because arthritic changes and spine spondylosis changes occur gradually over time. That's just a background.

Next, we have the issue of putting the needle in the disc, which by itself actually is a model for degeneration, for inducing degeneration. Nobody's talked about that. It's been in the discography literature, and that's a big reason why discography is way down now compared to what it was 10-20 years ago.

So we need to keep in mind that with our inducing a needle, and then injecting a specific thing to eat out the natural environment, which is taking away the chondroitin, we're basically accelerating degeneration for the short term of

relieving leg pain. We have no idea whether these patients are going to be back-pain cripples in 5-10 years down the road, and without longer term follow-up, we can't really determine that. Does it help leg pain in the short term? I agree.

DR. BATEMAN: So to the last clause of the question, whether additional data are needed to adequately assess the risk, you're saying, yes, additional data would be needed with longer term follow-up.

DR. KIRKPATRICK: Right. This is predominantly an anesthesia and drug-related group that is probably used to looking at short term. Unfortunately, we're looking at long term because I'm going to see the patients five years after the folks over in Winter Park because they're going to be coming in with their back pain; actually not, because they're not vets.

DR. BATEMAN: So we're hearing one perspective, that the the follow-up data is inadequate given the the changes in the potential for disc degeneration or loss of disc height. Does

anyone on the committee have a differing perspective, that the the follow-up data are adequate, or additional commentary you want to offer on that question?

DR. STOJANOVIC: It's the same as with surgery, injuring the disc with surgery as well. So that's why you have modic changes, alternative to this treatment with surgery.

DR. KIRKPATRICK: Right. Modic changes are part of a natural history of degeneration. The question is the speed of them and the magnitude of them as you go on after you've dissolved what normally would have been left behind in a discectomy, because we don't take all the nucleus; we only take the nucleus that's in the canal irritating the nerve root. As you mentioned, you don't go digging around to get everything out anymore. We're just doing that limited disc section. So you're leaving nucleus in there that still has chondroitin and still has some of its hydrostatic properties, so it's not quite the same.

DR. STOJANOVIC: I just want to add that I

agree, as the study has shown increased disc degeneration with discography, that might not be the only reason that discography can decrease utilization because discography is used for some minimal invasion treatments. They are not used anymore, so that's the major reason.

There are a lot of controversial papers on this. Studies that showed increased disc degeneration with discography, they used 100 PSI over opening pressure. 50 PSI is used for normal discography test, and probably 1cc is producing way less than this --

DR. KIRKPATRICK: I acknowledge that point --

DR. STOJANOVIC: -- so it's not clear.

DR. KIRKPATRICK: -- but the issue is that if I was to do a lab of degenerative disc disease, what I would do is I would stick a needle in the disc of the animal that I'm choosing, and it will degenerate, specifically related to just having the needle there; no drug at all.

DR. BATEMAN: So I'm hearing this is a

pretty significant concern, so it'd be good for others to weigh in.

DR. SCHIFF: So I appreciate this discussion a great deal, and it is important. I would ask whether, if approved, can the FDA plan to collect these long-term data? Remember also, these are relatively young individuals, and if we're creating problems we don't have evidence for now as these people go through their lives, that sounds critical to me. But I ask those at the table who know about disc --

DR. BATEMAN: Dr. Doshi, do you want to comment?

DR. DOSHI: There are different mechanisms for tracking what happens after a drug comes to market in terms of safety signals, and there are many different mechanisms that we can do that. Certainly, we are considering all of those in our review of the product. But there are ways to look at these things long term, yes.

DR. BATEMAN: Dr. Kennedy?

DR. KENNEDY: So, I'll weigh in and really

echo what's being said to this comment. This was probably my major concern with this. As I mentioned earlier, you are starting the degenerative cascade or maybe accelerating it. I, fortunately, was a little reassured. I mean, I do think that the data is strong, that it does have at least a modest effect on radicular pain in the short term.

The question then comes, when we look at the data on low back pain, it doesn't appear that there's a big increase, at least in this short duration on it, that is significant, and some of the longer term studies we have on it, were reassuring. That being said, I completely agree with earlier comments that we're going to need 5, 10, 15-year data to really see the long-term applications of this, and that is a very high bar if that is the standard we're setting.

I do think you would have to really watch this, and to be honest, I find myself asking the question, if I had a 35 year old, or my 35-year-old self when I herniated my disc, how interested would

I be in this, looking at the next 70 years, hopefully. Over. Thank you.

DR. BATEMAN: A very brief comment from the sponsor.

DR. REICH: I mean, we do have the Japanese real-world data to benchmark off of, so we can --

DR. STAUFFER: That's what we'd like to show you.

DR. BATEMAN: Yes. Okay.

DR. FUERST: Tom Fuerst, radiology. I just wanted to remind the committee about the longer term data that we have available. There was the survey that was done from the Japanese phase 2 study and phase 3 study that did follow additional patients out to 2 years and to 5 years following their condoliase treatment; and a reminder there was no increase or there was apparent benefit in terms of delaying surgery in the patients that were treated with condoliase.

On the imaging side, we didn't see any additional changes, any additional loss of disc height. Modic changes of type 1 became less

frequent, and we had more modic type 2 changes. Modic type 2 changes are less commonly associated with pain compared to modic type 1.

In addition, FDA pointed out there are 37 patients from the Japanese phase 3 study that were looked at, at 10 years after condoliase treatment. Amongst those 37 patients, five of those patients had surgery discectomy after condoliase treatment. Two of those were within the first year; one of those was at 2 years; two more were just at 5 years. One of those patients had a revision discectomy at 9 and a half years, so there's not a significant increase in surgeries in those patients that were treated out to 10 years.

Looking at the imaging data, the disc height from year 1 at the end of the trial until 10 years advanced further, from a 15 percent loss to a 20 percent loss in those ensuing 9 years after the trial ended; so some additional information to consider in terms of long-term effects of condoliase.

DR. BATEMAN: Okay. Thank you.

DR. KIM: Kee Kim, neurosurgery. I also want to provide the surgical perspective because as we talked about, and also committee members have recognized, what we're talking about are patients who have tried non-surgical treatments, who show on the MRI that they have a herniated disc and clearly explains their symptoms, and they are an appropriate candidate for surgery.

So we're talking about condoliase hopefully allowing patients to avoid surgery. And if you look at the surgical data, and even the best hands, there are going to be associated complications. If you have a complication such as nerve injury, that's pretty devastating. Spinal fluid leak, that's another common complication. So I do want to point out there are also risks associated with the surgery, and those things can also lead to other things in the future that was pointed out that may require additional surgery, including adjacent segment disease we didn't really even talk about.

DR. BATEMAN: Okay. Thank you.

Other comments? Dr. Nelson?

DR. NELSON: Actually, for Dr. Kim and Dr. Fuerst, just a follow-up on what you are discussing. Explicitly in discussion question 3, we talk about if condoliase affects surgical options or outcomes. Sorry; you were giving us a lot of data.

DR. FUERST: Yes.

DR. NELSON: I was trying to parse it as you discussed it. understand that condoliase treatment reduced the likelihood that they would have surgery, but what were the outcomes of the groups that had surgery? Were they quite similar?

DR. FUERST: Yes, in terms of the outcomes, in terms of pain relief?

DR. NELSON: Well, of the subsets of both groups --

DR. FUERST: Yes.

DR. NELSON: -- when they progressed to surgery, were there any differences between that group, between those two groups, in terms of their recovery from surgery, complication rates?

DR. FUERST: Yes. I don't have specific information about their pain outcomes, but there were not differences in the AE events following their surgery. We have talked about changes in the vertebral body and the spine. Those are signal changes in the marrow. We didn't see any structural changes in the bone of the vertebral body or the spine that might have prevented certain types of surgeries from occurring. In the postmarketing Japanese data, we don't have any reports that surgeries were not able to be performed after the condoliase treatment, and sometimes that happened as soon as 4 weeks after condoliase treatment if the patient was recalcitrant to condoliase.

DR. BATEMAN: We'll come back to Dr. Kirkpatrick.

DR. KIRKPATRICK: This is actually just a follow-up question for the FDA team. I've been working in devices, so I don't really know what postmarket surveillance looks like with a drug. Can you give us an idea of what that would be?

Because if it's not able to track people and look at the fine things, I don't know how that makes a difference. So can you tell us what the postmarket surveillance would be?

DR. BATEMAN: So the question is, what would postmarketing surveillance look like in a drug like this, and would you be able to track for things like development of pain over time, things like that?

DR. KIRKPATRICK: Or do you just rely on MedWatch reports or something like that?

DR. DOSHI: There are different levels of postmarketing studies that can be conducted, so we are considering all of the different options. It could range from everything to, as you described, MedWatch reports versus requiring a formal study as in the form of a postmarketing requirement, where it could be prospective, retrospective. The whole gamut is a possibility.

So when we decide what kind of study we would ask for or require, we really want to know what is the question and is that study going to

answer the question that we have. This is a really helpful discussion, and I really appreciate it. And what we are looking to discern from this discussion is whether additional data are needed, and what exactly that data would be in order to help us decide what these postmarketing studies could look like if we were to consider them.

DR. BATEMAN: Great.

DR. KIRKPATRICK: Some specifics, he mentioned that they have data on patients that had surgery, so surgeries in post-condoliase patients would be number one. If you could get ODIs, if you can get leg pain assessment, either VAS or something like that, you need to look at that at 2 years, 3 years, 4 years to know. And you can't just do it based upon the reported surgeries because patients will go from their pain management doc, to another doc, to another doc, to another doc, until they find one that's going to help them. And how do you then track that to get back to saying, "Okay. That patient failed?"

I would think surgeries would be number one.

If you can, follow them prospectively and get X-rays and MRIs at probably 2 and 5 years, that would be a really good combination of things, saying, "Okay. Well, if they're the same, then they're the same." I guess you guys as regulators have to decide if that is too burdensome or not.

DR. BATEMAN: That's useful input to the FDA in terms of potential future postmarketing surveillance, but I'd ask the committee to just reflect on the current state of data, whether the longer term risks have been adequately addressed and is the follow-up data from the Japanese population reassuring.

DR. KIRKPATRICK: Well, I understand that -- what was it? -- 10 patients were tracked, and six of them had surgery. Is that what I remember?

DR. FUERST: Out to 10 years, 37 patients --

DR. KIRKPATRICK: Okay. And how many had surgery?

DR. FUERST: -- and five of them had

surgery.

DR. KIRKPATRICK: Thank you.

DR. BATEMAN: Dr. Kennedy?

DR. KENNEDY: I was commenting earlier on future studies, and then we redirected it. But the longer term studies out of Japan are reassuring, maybe not completely sufficient, but definitely reassuring. They do help me in some ways. I think if I was looking at long-term surveillance, I do think surgical rates are a key. I would ask simply questions of pain scales and subsequent utilization of treatments, meaning if they are needing lots of treatment, opioid medications, and having lots of back pain in a different way, that's really what we want to know.

While imaging would be nice, I think this technique has been demonstrated to decrease the disc height, and I would expect that to be decreased. It'd be nice to know subsequent development of spondylosis, but you're really going to take a while to develop that and figure that out. It would be hard to do.

DR. BATEMAN: Any other comments on question 3?

(No response.)

DR. BATEMAN: To summarize, I think there was some concern voiced by members of the committee about some of the disc changes that are observed, expected changes but nonetheless changes that could increase risk for future arthritic changes or spondylosis. The Japanese data with longer term follow-up is somewhat reassuring but perhaps not as comprehensive as what we might hope. There's a feeling that if this is to go to market, that it would be useful to have long-term follow-up studies to assess safety with respect to axial back pain and other complications associated with degeneration.

Anything else to add to those points?

(No response.)

DR. BATEMAN: I guess just adding to that, the feeling that, really, short-term resolution of radicular pain is good, but what we really need to be looking at are changes at 2, 5, and 10 years in

order to fully understand the safety of the drug.

Okay. We'll go to question 4 next.

You were going to say something on 3 before we move on?

DR. STOJANOVIC: No.

DR. BATEMAN: Question 4, given the route of administration, the narrow population in which the drug has been established to be effective, and the potential risks of both the product and the procedure, discuss appropriate proceduralist and setting requirements to support safe administration of the drug.

Any clarifications on this question before we discuss?

(No response.)

DR. BATEMAN: Dr. Kirkpatrick?

DR. KIRKPATRICK: I'm sorry to keep bringing different things up or being the start of it, but I would like to know from the pain colleagues, do you have credentialing issues in your centers? Are you doing it in a clinic? Are you doing it in an outpatient center, that sort of thing? They would

have credentialing issues and that sort of thing.

I would also think that an interventional pain management physician would be schooled in various approaches to the spine with a needle, so I don't think that needs any special qualification, although I'd prefer those in that profession to comment.

Then finally, I think, as we heard, with the very rare exception of an anaphylactic problem or something like that, it sounds like a code cart would be a minimum, with oxygen and that sort of thing, which is why the setting, again, is probably a big deal. Any place that's going to be able to do conscious sedation probably is the key because they have the ability to have a code cart and that sort of thing. So I'll leave that to the pain physicians to comment.

DR. BATEMAN: Dr. Stojanovic?

DR. STOJANOVIC: Yes. Thanks. I just have to say, I was fortunate to have experience in discs. I started doing discography, introduced it to Boston and organized a large course on

discography in that time, as I did present a couple of other procedures that we did. So I did quite a few, a couple hundred discographies and other treatments, and wrote review papers on this and some prospective studies.

The procedure's relatively simple, but actually it's not. It's one of the most complex procedures that we have. Even technically, it might be difficult, especially the L5-S1 level, where you have a large iliac crest in the way, and you need to use the curved needle to go around, and probably use the double-needle technique in order to avoid the infection.

The infection rates, if everything is carefully done, naturally, are relatively very, very low, although for discography, usually intradiscal antibiotics are used. As I've seen it, these studies, they use IV antibiotics and are not mixing antibiotics with treatment, but the infection rates without intradiscal antibiotics are also very low. It's necessary to have extra levels of precautions with using gowns and everything

else, sterile draping as opposed to other procedures to avoid infection.

It is not a procedure that easily can be done by any interventional just to jump into. It's not a surgery, and I don't think any special privileges, but there has to be some kind of education at least warning that practitioner needs education in some way to do this, cadaver courses and some other ways to get to that level. They're not doing it routinely. It's not just jumping and doing it. That's something to think about.

Concerns that we heard about discography, FDA changed Study 1133, as we just heard, and placebo, we have saline to sham just because of these concerns. So yes, it's a relatively simple procedure. It's definitely simpler than surgery. It looks simpler than some other procedures like stimulator trial, but actually it's not. That's my comment.

DR. BATEMAN: Other comments?

Dr. Sprintz?

DR. SPRINTZ: Thank you. Michael Sprintz.

Yes. Really, the only thing I wanted to state is, although the majority of people probably doing this procedure in the future would be interventional pain providers, there are other specialists, for instance, spine surgeons and others, who do some of these procedures as well and are clearly capable of managing it. So I just wanted to express both caution in limiting the actual definition of the proceduralist based on specialty because there are multiple specialties that could do this.

Exactly what Milan talked about was, also on the other end, not everyone who may be an interventional pain doc has any experience, especially given the fact that interventional disc procedures have really fallen off, so some level of training also would be helpful. Then, really, the proceduralist, the ability to handle the complications associated with this would be really significant.

So either the ability to handle if something goes wrong, both the hypersensitivity aspects and wherever it's being done, and having the ability to

have resuscitative equipment I think is more important than, oh, it should be a hospital, or an ASC, or an office, or whatever. But the equipment available wherever this is being performed needs to be to a standard to do resuscitative emergencies to treat anaphylaxis if that's our immediate worst-case scenario. Thanks.

DR. BATEMAN: Thank you.

Other comments? Dr. Schiff?

DR. SCHIFF: Were any of the SCAR or apparent anaphylactic reactions immediate at the point of injection? I heard figures of 2 days and longer to develop that. If that's the case, in the 29,000 patients that have been looked at postmarketing, how strongly would we feel that you have to have that capability at the time of procedure?

DR. BATEMAN: Okay. A quick clarification from the sponsor on the anaphylaxis piece.

DR. MARTIRE: Diane Martire. There's one case that occurred within 20 minutes of injection. The patient's blood pressure went down and required

epinephrine.

DR. SCHIFF: Thanks. That answered my question.

DR. BATEMAN: Mr. O'Brien?

MR. O'BRIEN: Joe O'Brien, anecdotal and personal. I've had experience personally with both radiculopathy and a discogram, and I would say that despite having 6 spinal fusions infused to my pelvic, the most painful procedure I ever had was the discogram, by far. I would not give the opportunity to have condoliase because I would choose surgery. But that's me. That's clearly personal.

DR. BATEMAN: Dr. Nelson?

DR. NELSON: I was just going to add clarification for Dr. Kirkpatrick that my impression is that most pain clinics, even if they are not offering sedation, do have code cart capabilities and ability to treat anaphylaxis. My pain clinic in particular, we don't offer sedation, but we have code carts, too.

DR. BATEMAN: Dr. Kirkpatrick?

DR. KIRKPATRICK: I put it down.

DR. BATEMAN: Sorry. Okay.

Dr. McAuliffe?

DR. McAULIFFE: Yes, I'd like to respond to that, too. Even though there are code carts there, unless these places are accredited, they're not practicing. They're not exercising those code carts, making sure that they know what to do with them; that the people there that are credentialed know how to manage a crisis. So it's not just that that's there; it's there and it's a credentialed institution.

DR. BATEMAN: I have a question for members of the committee. In our briefing document from the FDA, they talked about the history with the drug chymopapain, which if injected into the subarachnoid space would cause subarachnoid hemorrhage. How much of a risk of ending up inadvertently in the subarachnoid space is this procedure, and what are the precautions that could be done to ensure that doesn't happen?

DR. STOJANOVIC: Yes, very low.

To tie up the comment of Mr. O'Brien that this was the most painful procedure, actually, in the very beginning when it started, it was painful to use IV sedation, as you mentioned, and we haven't used IV sedation almost ever. So it's a highly technical procedure. Someone has to do something really, really bad intrathecally.

But it's easy to hit the nerve root. It's sometimes frustrating passing the nerve root. One has to inject a contrast to see the nerve root to bypass it. Some rare cases, it can be complex, so it needs really high and technical expertise. If it is not, it can be painful, and if it's extremely not, it can result in these kinds of cases; unless there is a rupture of the disc, which we discussed in the very beginning, and that's where I commented. So that said, it should not be done with large radial tear of the annulus.

DR. BATEMAN: Dr. Nelson?

DR. NELSON: So a difference, though, between, my understanding, discography and this indication would be that with discography,

oftentimes you are attempting to ascertain which disc is causing the pain, so the patient does not receive sedation, whereas in this case, they could receive sedation.

DR. STOJANOVIC: The most painful part of the procedure is getting to the disc, and just injecting in the disc, usually discography is done 3 levels, 1 and 2 controls. Two controls should not cause pain. Pain that's reproduced should usually be concordant, and it should not be much worse than regular pain. This is not the same thing where we're pushing the disc out. It's just for internal sensitization of the disc, so that part is not that painful.

DR. NELSON: I think I'm agreeing with you. I'm just trying to allay Mr. O'Brien's fears that this would be an extremely painful procedure because you could receive sedation, and it would not be attempting to provoke a concordant pain response.

DR. BATEMAN: One more comment on this question, and then we'll move on.

Dr. Bicket?

DR. BICKET: Thanks. Dr. Stojanovic's comments brought up a thread that we had earlier discussing about this drug product potentially mixing with others, including contrast. And it seems, given the individuals who would be performing the procedure, that that mixing could likely happen. This may just be an area of, if I'm thinking about supporting the safe administration of the drug, having some data or some statements for the community to understand in the event this drug product is approved.

DR. BATEMAN: Okay. Just to summarize here, I think a major concern with the administration is the potential for anaphylaxis. So if the drug's going to be administered, it needs to be done in a setting where there's the ability to treat anaphylaxis, where you have a code cart and other resuscitative equipment that would be required to treat anaphylaxis.

I think there was an expression that this does require some technical competence in that that

there would need to be courses or other venues for teaching pain positions and how to safely give this injection. Then finally, the point was made that people may want to mix the compound with contrast, so doing safety studies to ensure that those are compatible would be important, given how it will likely be used in routine practice.

Anything else that I missed?

(No response.)

DR. BATEMAN: Okay. We'll move on to question number 5. Discuss the level of concern for immune-related adverse reactions, including hypersensitivity, anaphylaxis, SCARs, as well as appropriate mitigation and monitoring strategies.

Any questions about the the wording?

(No response.)

DR. BATEMAN: Okay. Then, Dr. Reich?

DR. REICH: Just one question, a legacy question from earlier on this topic, though, for the sponsor. Were the SCARs all from the Japanese population, and if so, was there any manufacturing variances that you could characterize that came

from a certain batch or a certain manufacturer that we're no longer using; that kind of thing?

DR. MARTIRE: Diane Martire. By definition, these were all postmarketing events, so they are all from Japan. For the solicit reports, we did capture batch, and there was no correlation with batch. For the unsolicited, we don't have that batch information.

DR. BATEMAN: While you're at the microphone, can I just ask, how many of the SCARs came from the solicited reports?

DR. MARTIRE: One of the AGEP. It's about half.

DR. BATEMAN: Half. Okay.

DR. MARTIRE: About half, yes.

DR. BATEMAN: So 2 to 3 out of 4,000.

DR. MARTIRE: Yes.

DR. BATEMAN: Okay.

Other comments?

(No response.)

DR. BATEMAN: So I'll ask the committee, we have reports of 2 to 3 potentially

life-threatening, severe cutaneous adverse reactions, a source population of 4,000. Is that something we should be concerned about?

Dr. Schiff?

DR. SCHIFF: A related question to that is how to avoid these very serious complications. In the data from the company, they mentioned skin testing after one of these events, which proved positive and helped document that the drug appeared causal. The other issue is, I don't see how you can study an event that rare asking if, for instance, steroid administration in advance of injection is going to be preventative.

Would it be an option for people to opt for skin testing prior to injection? And a corollary question, would the skin testing potentially sensitize those individuals? I don't know enough about immunology.

DR. BATEMAN: I think it's an important question, so maybe we could hear from the sponsor on that.

DR. MARTIRE: Diane Martire. We've

consulted with an expert in SCAR about this, and there are pros and cons about patch testing, skin testing. Skin testing could potentially evoke anaphylaxis in a susceptible patient, and there is no standard for patch testing with a new drug, so the standards for patch testing also are very variable. We at this time don't have a way to predict or to mitigate the risk. We see no commonalities, and there are none available.

For the cases of AGEP, which we saw, which were biopsy proven, for AGEP, there's currently no known genetic marker other than perhaps a variance in genetics for IL-36. It's not like some of the other drugs that you have a genetic marker you can test preemptively. It's not been identified to date. We've looked exhaustively at this to see if there is anything we can do to predict or mitigate, and at this point, there is nothing certain.

DR. SCHIFF: Thank you.

DR. BATEMAN: Thank you.

Other comments?

(No response.)

DR. BATEMAN: The question is the level of concern. So if we have an event rate of 1 in 1500, 1 in 2,000, what is the level of concern associated with that? It's important to give FDA feedback on that.

Dr. McCann?

DR. McCANN: Mary Ellen McCann. Well, I think the sponsor just answered the question whether there's mitigation, and I guess there's not. So then the question becomes, what monitoring strategies should we invoke for the future of this, and open that up to the committee, or what does the FDA usually do for drugs that may be at high risk for SCARs?

FDA can answer that.

DR. DOSHI: So, as I was saying before, there are a range of different things that we could consider, but I would say that those are outside the specific scope of what we're asking for here in this question. What we're really looking for are monitoring strategies in the moment with administration of this drug. So the longer term

studies and questions that you're asking about are outside the scope of what we are trying to get at with this discussion.

DR. BATEMAN: Dr. Schiff?

DR. SCHIFF: So, I'm concerned. These are serious reactions. I could envision, I don't know, the next few years, a million people might get this therapy. You just used a number of 1 in 1,000. Ouch! A few hundred of these cases in the U.S. would likely cause the FDA to think twice about continuing approval. So, I don't have the answer to this. I very much appreciated the doctor's comment about the existing evidence and data to prevent and/or mitigate these these reactions, but I'm quite concerned that we're heading into larger numbers with wide-scale adaptation.

DR. BATEMAN: Yes.

DR. DOSHI: There are other things beyond what he was just talking about in terms of this discussion, things that we have considered and will be considering; as has been alluded to, what can go in the labeling and what should be in the labeling,

and to maximize the appropriate patient population, monitoring, and mitigation strategies that we're talking about here.

The other thing that we haven't touched on as much is this concept of pharmacovigilance, which is a step above waiting passively for reports about safety to come in, and being extra "vigilant," to use the word, about particular concerns that have been brought up here if the product were to enter the market.

DR. THANH HAI: This is Mary Thanh Hai. I was going to comment in the similar sense that Dr. Doshi added. We understand that this is very challenging because when a marketing application comes in, you have very limited information premarket, and these adverse events, you're correct to not dismiss it. And certainly, this is something that we often would definitely include in labeling to make sure that a prescriber and a patient are aware of the risk to weigh that with the benefit. But it doesn't stop there. Once a product is approved, you have adverse events that

have to be monitored and reported to the agency. And we could actually work with the company with respect to the amount of information we need, the time frame in which this is going to actually be provided.

Certainly, there have been other products, as you have noted in the conversation today, that have been associated with these types of reactions. Luckily, they're not a lot, but they have yet remained on the market, and at times, we will make changes to labeling to make sure that it would be appropriate with new data that come in. Thank you.

DR. BATEMAN: Other comments?

Dr. Nelson?

DR. NELSON: As far as immediate hypersensitivity reactions, we already monitor for that in interventional pain settings because of the high rate of hypersensitivity reactions to contrast dye, but as far as the 48 hours later type of adverse reactions, it would probably be something along the lines of a different strategy.

DR. BATEMAN: Dr. Bicket?

DR. BICKET: Thank you. On the topic of these immune-related adverse reactions, I did appreciate the presentation by the FDA and Dr. Sudhakaran's insights about the relative level of SCARs and other adverse reactions that happen with some types of prescription medications, including those that do have high rates. While we have some initial data at this time, I think it does have a lot of concern, though.

To me, this would be something that would be appropriate to include, again, were you to have the drug product approved, with this risk profile, to then consent, and then have a discussion with the patient about these potential risks and benefits. But when it comes to monitoring longer term, it certainly would be helpful to have greater clarity about what that looks like, especially in the population of patients in the United States who undergo this, given we see some differences in terms of the studies that have been submitted relative to the performance in the Japanese population. Thank you.

DR. BATEMAN: Dr. Kennedy?

DR. KENNEDY: The SCARs are a concern. It really depends upon the rate of them, and I think part of the question would be the comparator. We're talking life-threatening reactions, and I think you do have to compare this to a microdiscectomy or a single-level laminectomy. Those are not having 1 in 1,000 people with life-threatening reactions. You can't compare this to overall spine surgery. I mean, this is not a 3-level level fusion we're talking about. If it really is 1 in 1,000 and 1 in 1500, we're going to figure that out very quickly, and that's the good news.

I did, earlier, some back-of-the-math calculation, just going off of the presenters' numbers, where if you estimate 250 million adults in the U.S., 1 to 3 percent, and 20 to 50 percent of those being potential candidates for this, and then you do a 1 in 5,000 reaction, you are talking somewhere between 83 and 600 reactions a year. And that's off the 1 in 5,000 number, and that's using

those numbers; a lot of big assumptions there. The beauty of it is we would know quickly, and it would have to be something that we would have to follow very quickly and compare it to the other treatments.

DR. BATEMAN: Dr. Reich?

DR. REICH: Yes. And by other treatments, I think it's fair to include oral solids, those drugs, antibiotics, anticonvulsants. The rates and incidence of hypersensitivity, severe hypersensitivity, in those classes are nothing, so they're probably in the same, if not higher, rate per thousands, I would venture. That data should be gettable and knowable.

DR. BATEMAN: Dr. Schiff?

DR. SCHIFF: I think his question is a very good one. My impression looking at the FDA document was that our currently approved pharmaceuticals have a lower rate than what we're now discussing in terms of these SCAR events. Is that true? Do we have approved drugs that go as high as, let's say, 1 in 1500?

DR. DOSHI: Just to clarify, actually, in the briefing document -- and I'm sorry if this wasn't clear from it -- the rate that we're seeing here is actually comparable to approved products on the market; however, Dr. Sudhakaran touched a little bit on the difficulty of actually tracking the true rate of these adverse reactions, both for this product and for other products.

Now, what I will say is the other products that we have, that we're comparing against that Dr. Sudhakaran mentioned -- like the anticonvulsants, the NSAIDs, some of the others -- they have a pretty high prevalence of use, so the total number of cases is going to be larger. There is more of that data. At the same time, the fact that they have that risk of SCAR or other cutaneous reactions has not risen to the level that they've needed to be withdrawn from the market, so that is something that they are labeled for.

DR. SCHIFF: A related question -- again, I'm out of my lane here, but from reading your

documents -- is there a known higher rate in East Asian populations; therefore, would we expect in the more diverse U.S. population, that's an upper bound and perhaps we'd see lower rates?

DR. DOSHI: That's possible. Something that we did consider is the fact that in certain drugs where there is a higher rate of these severe cutaneous reactions, there is a known association being of East Asian descent and having these reactions; however, we don't have enough data here in this population, either from Asians or non-Asians, to really draw that conclusion, but that's for other drugs.

DR. BATEMAN: It seems to me, the calculation of the SCARs rate is dependent on a lot of assumptions. If you look at just the 4,000 patients or 4,000 administrations, where patients were surveyed, the rate is quite high, 1 in 1500, 1 in 2,000, and maybe higher than most of the drugs that are on the market. If you look at the larger population, the 29,000 or whatever that received the drug, the rate falls, but there you're really

dependent on spontaneous reporting, which we know is generally undercounting these kinds of adverse events.

I guess the other thing, these severe adverse events really need to be balanced against the benefit of the drug. If you're balancing it against the highly effective antiepileptic or highly effective antibiotic, it may be a different risk-to-benefit calculation than against a pain treatment that has more modest benefits.

Other comments? Dr. Sprintz, did you have your -- oh, okay.

Just to summarize, we had a good discussion about these immune-related adverse reactions. We heard from the sponsor that there currently isn't an approach to pre-exposure testing that could be reliably used to predict who's going to have a serious adverse reaction. I think some of the committee members, perhaps more than others, were quite concerned about the rate, and in many ways, we don't fully know the rate based on the available data. I think there's a general feeling that this

is something that, if the drug were to be approved, would need to be closely monitored in the postmarketing surveillance period.

Additional points on this?

(No response.)

DR. BATEMAN: Okay. Then, I think we'll move to our voting question. The voting question before us is, do the benefits of condoliase injection for the treatment of radicular leg pain associated with confirmed nerve root impingement caused by lumbar disc herniation in adults with radicular leg pain outweigh the risks?

Then, after your vote, you'll be asked to provide a rationale for your vote. If you voted yes, specify the evidence that establishes condoliase's effectiveness and safety. If you voted no, provide recommendations for additional data that may support a conclusion that condoliase is safe and effective.

DR. SPRINTZ: This is not necessarily the question in the total labeling because I know that we've talked about changing the labeling, so I want

to make sure. Does our answer to this question define what the labeling would be? Let's say I vote yes, then that would be what the labeling would be versus as we've talked about?

DR. BATEMAN: So I'm going to say, in your comments, you can provide suggestions for what might be contained in the label, if you vote yes. Is that a fair --

(Dr. Sprintz gestures yes.)

DR. BATEMAN: I'm going to give the instructions for the voting question. We'll now proceed to our last question, question 6, which is a voting question. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the

vote will be locked in. The vote will then be displayed on the screen. The DFO 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 vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all questions have been answered or discussed.

Any clarifications to the question before we vote?

(No response.)

DR. BATEMAN: We can proceed with voting. Please enter your vote.

(Voting.)

CDR BONNER: LaToya Bonner. For the record, for question 6, 8 yeses, 4 noes, 0 abstain. I will now turn the floor back over to our chair, so we can go around the table and speak our votes and justifications, if we choose to. Thank you.

DR. BATEMAN: We'll go left to right.

DR. KIRKPATRICK: I think my justification

was mostly in my comments.

DR. BATEMAN: State your name and your vote, please.

DR. KIRKPATRICK: Sorry. John Kirkpatrick. My vote was no. Most of my reasons are within the comments that we've already talked about. The principle is the concern for the patients accelerating their degenerative process and ultimately having either more back pain or more degeneration, or both. It's a razor-thin decision that I had to make, and I thought of the patients that I see on a day-to-day basis. Degeneration typically is bad, and I don't want to progress it to try and treat a short-term leg pain. I also assume that the FDA will take into consideration the discussion that we had on the indications, and making sure they're clear and very specific. Thank you.

DR. SPRINTZ: I am Michael Sprintz, and I voted yes with an asterisk in terms that I voted yes, one, that the studies in 1031 and 1033 I felt supported efficacy and safety. I think the biggest

caveat that I have on my yes is that the labeling will consider a narrower scope of not only just confirmed nerve root impingement, but also failure of conservative therapy. And I know that there's still a discussion going on in terms of back versus leg pain, but I definitely think that that needs to be looked at seriously before finalizing the labeling.

I do like the the concept in terms of the patient handout about hypersensitivity reaction, and especially because the vast majority of these reactions occur after the patient has already left, 1 to 2 days later, up to 8 days later. Therefore, I think even though there is a level of seriousness and I think the monitoring is important as ongoing, I don't think the incidence was enough for me to say no to that, and especially because all of those were treated successfully from that. So that's what I have. Thank you.

DR. McCANN: My name is Mary Ellen McCann, and I voted yes. I think the sponsor made a case for this drug being efficacious with narrow

indications, and I think within those narrow indications, there are a group of patients that just are not willing to have surgery; and for those patients, I think this drug is indicated for this use.

I do think that we need robust postmarketing surveillance. The experience in Japan is only 7 or 8 years, maybe 10 years. I do worry about arthritis, but I don't know that we have any evidence yet that the arthritis or acceleration of degenerative changes would be greater with this versus surgery. So I think we need more data down the line, but right now, I voted yes.

DR. STOJANOVIC: Yes. Milan Stojanovic. I voted yes. Also, it wasn't an easy decision, but I considered the vacuum between conservative care and surgery, for radicular pain and potential complications in surgery. Studies 1031 and 1133 show positive outcomes, but I just want to highlight by a narrow margin, a very narrow margin. So it was very difficult to make this decision.

Condoliase is minimally invasive opposed to

surgery. I think close monitoring, as discussed, for hypersensitivity is very important, especially a year or two because of numbers, as D.J. Kennedy mentioned, and also long-term monitoring for modic changes. My rationale will be the vertebrogenic pain due to modic changes, which will be most common with this, not discogenic, but vertebrogenic, and is actually now in focus, in large focus, so everyone is paying attention to this. So it'd be relatively easier to pick up if a high incidence of vertebrogenic pain occurs.

Although I agree with the comment that the company presented, a narrow indication for this, I think the indication should be even more narrow. There is huge room for improvement. The biggest problem with this is this can be used for anyone. It's very easy to call anything radicular pain. It should be radicular with corresponding dermatomal distribution, clear nerve compression, not by spinal stenosis; no weakness, motor, and sensory deficit; minimal invasive intervention; considering excluding complete radial tear and nucleus leak;

and considering not narrowing either the younger patient population, or younger disc or relative age. Then, the final two things are to make it clear that this is not approval of cervical and thoracic indication for everyone and the need for education for proceduralists.

DR. McAULIFFE: Hi. It's Maura McAuliffe. I voted no. I was concerned that the modest benefit, as I saw it, with all the exclusions surrounding the studies, especially 1133, did not balance the potential acceleration of degeneration in the back, and that we don't know in 2, and 4, and 6 years. I'm also concerned, if this is approved, that there are many, many pain clinics throughout the United States. They are not the same. They are not staffed the same way. They are not accredited the same way, and I'm concerned about where this drug is going to be given, in offices here or there, and that needs to be looked at. Thank you.

MR. O'BRIEN: Joe O'Brien, and I voted yes; and oddly enough, all of the same reasons that she

voted no.

(Laughter.)

MR. O'BRIEN: I think at the end of the day, in looking at it, there is a real need out there. There's clearly a cohort of patients defined very narrowly here. So if we're looking at the question very narrowly for that cohort of patients, I've been there, I've dealt with it, I know what it's like on their activities of daily living. There needs to be another tool in the armament of non-operative care. I think that's very valid to have.

On the other hand, as I said in my comments earlier, I am definitely afraid that the negative 1131 study is an omen of things to come. Even if you took all 4 pages on 1133 and put that into a labeling, that is not going to prevent this from proliferating well beyond what the patient should be; and we don't know what's going to happen, except for the negative study that we see in 1133, and I am deathly afraid of if that happens. So I think, as much as possible, to keep it within that

very narrow definition of what we have in the patient population. I just don't see how that's going to happen.

DR. BICKET: Hi. I'm Mark Bicket. I wanted to thank everyone for the opportunity to review these studies, presentations today, and the hard work from the sponsor, the perspective from the FDA, and I think also the insights from many of the members of the committee, which I really respect. It's an honor to learn from everybody here today.

I voted yes, and I believe the product does address an unmet need and the treatment pathway of lumbar disc herniation for patients who haven't adequately responded to conservative therapy of at least 6 weeks and who may be considering surgery but may not be eligible for that, or may not wish to pursue that. I do think the product has the potential to be meaningful for patients, in particular, given that there are many reasons that some may not be able to pursue surgery.

The two studies, to me, do appear to support the use of the products in a select patient

population with lumbar disc herniation. I did find the learnings from the negative study to help inform the label to be very challenging and would instead likely rely on characteristics from the positive study done for persons in the United States, 1133, to be more appropriate in terms of making modifications to the label.

It was brought up earlier about the type of herniation, and that's very important to clarify. We had a couple clarifying comments about different aspects of the spinal, neuroforaminal, the canal anatomy and its impact in terms of patient selection, and I do believe that those are important. Things that need to be clarified, in particular, when we think about selecting patients for the procedure.

I do think safety concerns -- we've discussed them -- the back pain, in particular, about the week after injection, was important and I think appropriate to include in the label, these immune-related adverse reactions and MRI X-ray abnormalities. Those modic type 1 and type 2

changes, I think we still have a lot of questions in the field about those, and here. I wouldn't necessarily expect the sponsor to answer all those, but those to be worthy of study in postmarket.

Overall, to me, again, it's just the balance of these benefits and risks appearing appropriate for a select group of persons who have lumbar disc herniation, and then failing conservative therapy. I certainly do believe some changes do need to be made, and with these suggestions, I think that the task is not enviable and may be back on the FDA to work it out with the sponsor as it comes to that. Thank you.

DR. SCHIFF: Steven Schiff. I voted yes, taking into account all the reasons that we as a group have voted both yes and no. I think with the highly restricted data, this shows benefits greater than risks. I think that the benefits are relatively modest but, impressively, it decreased the number of subjects that felt the need to go on to surgery. I would approve this, if it is approved, with as much restriction to be aligned

well with what the clinical trial that was successful used because those form the best data we have for outcome benefits that are worth the known risks.

I also think, just as with lumbar spine surgery, it is broadly overused for weaker indications than were used in this clinical trial that was positive. I believe this drug will likely also be overused well beyond the indications, however they're specified. And if I were to choose between patients getting overused lumbar disc surgery versus overused minimally invasive injection, based on what we know today, without the long term effect on the spine and without an adequate follow-up for these severe hypersensitivity reactions, I think I'd rather see people get an injection than an inappropriate open surgical procedure. So that forms my rationale, and I voted yes.

DR. JOWZA: Hi. Maryam Jowza. I voted no, and it was not an easy no. I went back and forth quite a bit in my head. Part of the reason I went

with no at the end was the indication is quite narrow, and the effect, even with the very restricted study, is still fairly modest. And then when I weigh that against the potential risks for accelerated spine degeneration and issues down the line, on top of the possible adverse reactions that can happen with the rate of, quoted, "anywhere between 1 and 5,000 to 1 in 1,000," that made me say no. I think if I had more long-term data, that would have swayed me towards a yes.

DR. NELSON: Ariana Nelson. I voted yes, and I did so because my largest concern coming into this meeting was the degeneration of the disc, and I feel that through our discussions, my fears have been somewhat allayed in terms of the fact that the risk of modic changes is probably similar to even very minimally invasive surgery.

So my caveat would be, I think that the indication should specify that the patient not only failed conservative management as a broad vague comment, but that they failed 6 weeks of conservative management, which is a similar

indication that's required for authorization for radiofrequency ablation of the lumbar facet joints, for example.

I also did not feel that there was a safety concern that some brought up about clinicians not being adequately procedurally adept to perform this procedure, especially with increasing adoption of the advent of basivertebral nerve ablation. I think the psychomotor component of the procedure will be more common, and we'll have an increasing number of clinicians that are very facile.

Lastly, the concern with safety for hypersensitivity reactions and SCAR, contrast dye, which we use for nearly 100 percent of our procedures, has twice the rate of hypersensitivity reaction of what has been reported here today. So already in pain clinics, there is ample monitoring for immediate hypersensitivity reactions. There may be a higher rate of delayed hypersensitivity reactions. That's something that we should also take into account and monitor with this new drug.

DR. BATEMAN: We'll now go to Dr. Kennedy.

DR. KENNEDY: D.J. Kennedy. I voted yes. Before I get into the reasons, I do want to thank the sponsor specifically. This kind of work is challenging, difficult, and they did a series of good studies that represent good and honest science. I also thank the FDA for distilling this in a very usable format.

My yes vote was razor thin, as for all the reasons that have been expressed around the table, predominantly small effect sizes and concerns of adverse reaction. I did vote yes because I felt it was a tool for good doctors and a subset of patients, and I didn't want to regulate, even though less scrupulous doctors may be more common than we think. The data for effectiveness wasn't a very small subset of patients. Even though I see patients like this regularly, I personally won't be using this until I get a little bit longer term data on it so that I can effectively counsel my patients.

I think there are concerns over labeling. I would agree with the comments before in terms of

6 weeks failed conservative character and radicular pain are the indications because this can be broadly applied given the prevalence of disc pathology on asymptomatic MRIs that can be confounding variables.

I do have specific concern over significant reactions of SCARs and long-term degeneration, I think both of which should have specific post hoc marketing plans in place. They would be different because of the time frames for them. The SCARs should be readily figured out very quickly given the numbers we're talking about in the United States; that there's a difference in genetic predisposition in the replicated data.

Lastly, I do firmly believe that this will be overutilized. Unfortunately, I don't think that's a unique statement in the spine world, as almost every treatment we have is probably overutilized, and some. But I appreciate the panelists and sharing the panel with the rest of the panel. I learned from all of you, and thank you for your time and facilitating me being remote.

DR. BATEMAN: Before I read my vote into the record, I just want to thank the panelists for a really excellent discussion and really thoughtful comments during the day. I want to thank the sponsor and the FDA for really outstanding presentations. I think this was a good meeting where we gave some really helpful feedback to the FDA.

Brian Bateman. I voted no. It was a very close vote for me. I agree there is an unmet clinical need, and many of the patients who will potentially receive this medication would otherwise undergo surgery, which has obvious inherent risks. That said, ultimately balancing the safety concerns, which are not fully characterized at this point, against the modest and, in many cases, unclear benefits of the the drug tilted my vote to a no at this point.

I'm quite concerned about the rate of SCARs in the surveyed population of 4,000. There were 2 to 3 SCAR events, so a rate of 1 in 1500, 1 in 2,000, for a life threatening complication, that's

really quite a high rate, and I think that's something we need to get a better handle on. I agree with a lot of the concerns that the panel has raised around disc degeneration and the need for more robust long-term follow-up.

I'm concerned, like the other panelists expressed, that the population that will ultimately receive this may look a lot more like 1131 than the population that was enrolled in 1133. I think it's really going to be incumbent, if the FDA moves forward, to specify the indication in a very clear way, hopefully in a way that aligns quite closely with the inclusion criteria for the U.S. trial that did show benefit, as well as with a clear statement that patients need to fail conservative management prior to receiving this medication.

So with that, before we adjourn, are there any last comments from the FDA?

DR. DOSHI: No, but I wanted to take this opportunity to thank everybody here in this room for a really robust and helpful discussion that will really help guide us as we continue with our

deliberations on this product. Thank you all for your time and attention.

Adjournment

DR. BATEMAN: Okay. We will now adjourn the meeting. Thanks very much.

(Whereupon, at 4:19 p.m., the meeting was adjourned.)