FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE (AADPAC) MEETING

Wednesday, February 14, 2018

Day 1

1:30 p.m. to 3:55 p.m.

FDA White Oak Campus

Building 31 Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Moon Hee V. Choi, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE MEMBERS (Voting)

David S. Craig, PharmD

Clinical Pharmacy Specialist

Department of Pharmacy

H. Lee Moffitt Cancer Center and Research Institute

Tampa, Florida

Jeffrey L. Galinkin, MD, FAAP

Professor of Anesthesiology and Pediatrics

University of Colorado, AMC

Medical Safety Officer

CPC Clinical Research

University of Colorado

Aurora, Colorado

Jennifer G. Higgins, PhD

(Consumer Representative)

Director of Research & Policy

Association of Developmental Disabilities Providers (ADDP)

Framingham, Massachusetts

Ronald S. Litman, DO

Professor of Anesthesiology & Pediatrics

Perelman School of Medicine

University of Pennsylvania

Attending Anesthesiologist

The Children's Hospital of Philadelphia

Medical Director, Institute for Safe Medication Practices

Philadelphia, Pennsylvania

Mary Ellen McCann, MD, MPH

(Acting Chairperson)

Associate Professor of Anesthesia

Harvard Medical School

Senior Associate in Anesthesia

Boston Children's Hospital

Boston, Massachusetts

Abigail B. Shoben, PhD

Associate Professor, Division of Biostatistics

College of Public Health

The Ohio State University

Columbus, Ohio

Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP

Faculty and Clinical Instructor

Pain and Medical Ethics

State University of New York Stony Brook School of Medicine, Stony Brook, New York

Ethics Committee Chair

St. Catherine of Siena Medical Center

Smithtown, New York

TEMPORARY MEMBERS (Voting)

Gregory Terman, MD, PhD

Professor, Department of Anesthesiology and Pain Medicine and the Graduate Program in Neuroscience

Director, University of Washington Medical Center Acute Pain Service

University of Washington

Seattle, Washington

Padma Gulur, MD

Professor of Anesthesiology

Vice Chair, Operations

Department of Anesthesiology

Duke University

Durham, North Carolina

Laura D. Porter, MD

(Patient Representative)

Cancer Survivor Independent Patient Advocate

Washington, District of Columbia

ACTING INDUSTRY REPRESENTATIVE TO THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE (Non-Voting)

Michele Hummel, PhD, RPh

(Acting Industry Representative)

Pharmacist

Moss Rehab Einstein Healthcare Network

Elkins Park, Pennsylvania

FDA PARTICIPANTS (Non-Voting)

Sharon Hertz, MD

Director

Division of Anesthesia, Analgesia and Addiction Products (DAAAP)

Office of Drug Evaluation II (ODE-II)

Office of New Drugs (OND), CDER, FDA

Rigoberto Roca, MD

Deputy Division Director

DAAAP, ODE-II, OND, CDER, FDA

Alla Bazini, MD

Medical Officer

DAAAP, ODE-II, OND, CDER, FDA

David Petullo, MS

Statistics Team Leader

Division of Biometrics II

Office of Biostatistics (OB)

Office of Translational Sciences (OTS)

CDER, FDA

Yun Xu, PhD

Clinical Pharmacology Team Leader

Division of Clinical Pharmacology II

Office of Clinical Pharmacology (OCP)

OTS, CDER, FDA

C O N T E N T S

AGENDA ITEM	PAGE
Call to Order and Introduction of Committee	
Mary Ellen McCann, MD, MPH	10
Conflict of Interest Statement	
Moon Hee Choi, PharmD	14
FDA Introductory Remarks	
Sharon Hertz, MD	18
Applicant Presentations – Pacira	
Introduction	
Michael Rozycki, PhD	22
Unmet Need	
Anoushka Afonso, MD	29
Efficacy	
Roy Winston, MD	35
Safety	
Richard Scranton, MD, MPH	51
Clinical Perspective	
Jeff Gadsden, MD, FRCPC, FANZCA	61
Conclusion	
Richard Scranton, MD, MPH	69

C O N T E N T S (continued)

AGENDA ITEM	PAGE
Clarifying Questions	74
Adjournment	125

P R O C E E D I N G S

(1:30 p.m.)

Call to Order

Introduction of Committee

DR. McCANN: Welcome and good afternoon. I would first like to remind everybody to please silence cell phones, smartphones, and any devices if you have not already done so. I would also like to identify the FDA press contact, Tara Rabin. If you are present, please stand.

My name is Mary Ellen McCann. I am the acting chairperson of the Anesthetic and Analgesic Drug Products Advisory Committee, and I will be chairing this meeting. I will now call the meeting of the Anesthetic and Analgesic Drug Products Advisory Committee to order. We'll start by going around the table and introducing ourselves. We will start with the FDA to my left and go around the table.

DR. HERTZ: Good afternoon. Sharon Hertz, division director for the Division of Anesthesia, Analgesia, and Addiction Products.

DR. ROCA: My name is Rigo Roca. I'm deputy division director in Dr. Hertz's division.

DR. BAZINI: This is Alla Bazini. I'm a clinical reviewer in the Division of Anesthesia, Analgesia, and Addiction Products.

MR. PETULLO: David Petullo. I'm the statistics team leader supporting DAAAP.

DR. XU: Yun Xu, clinical pharmacology team leader supporting DAAAP.

DR. SHOBEN: Hi. I'm Abby Shoben, and I am an associate professor of biostatistics at the Ohio State University.

DR. CRAIG: Good afternoon. Dave Craig. I'm a clinical pharmacist specialist at Moffitt Cancer Center, Tampa, Florida.

DR. LITMAN: I'm Ron Litman. I'm a pediatric anesthesiologist at the Children's Hospital Philadelphia and the medical director of the Institute for Safe Medication Practices.

DR. CHOI: Moon Hee Choi, designated federal officer.

DR. McCANN: I'm Mary Ellen McCann. I'm

from Boston Children's Hospital as a pediatric anesthesiologist and an associate professor at Harvard Medical School.

DR. GALINKIN: Jeff Galinkin, and I'm professor of anesthesia and pediatrics at the University of Colorado and medical safety officer at CPC Clinical Research.

DR. HIGGINS: Jennifer Higgins. I'm the consumer representative to AADPAC.

DR. PORTER: Laura Porter, consumer representative.

DR. TERMAN: I'm Greg Terman. I'm professor of anesthesia and pain medicine at the University of Washington in Seattle and director of the Acute Pain Service at the University of Washington Medical Center.

DR. ZACHAROFF: My name is Kevin Zacharoff. My expertise is in anesthesiology and pain medicine, and I am faculty and clinical instructor at State University of New York Stony Brook School of Medicine.

DR. GULUR: My name is Padma Gulur, and I am

a professor of anesthesiology at Duke University. I'm also the medical director of the pain service there.

DR. HUMMEL: My name is Michele Hummel. I'm a pharmacologist, and I'm acting as the alternate industry rep.

DR. McCANN: For the topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be 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 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 and lunch. Thank you.

I will now pass it to Moon Hee Choi, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. CHOI: 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 of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not

limited to those found at 18 USC Section 208, 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 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her 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 interest of their own, as well as those imputed to them, including those of

their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves a discussion of supplemental new drug application sNDA 022496/S-009, for EXPAREL, bupivacaine liposome injectable suspension, submitted by Pacira Pharmaceuticals to produce local analgesia and as nerve block to produce regional analgesia. This is a particular matters meeting during which specific matters related to Pacira's sNDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing 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'd like to disclose that Dr. Michele Hummel is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Hummel's role at this meeting is to represent industry in general and not any particular company.

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.

DR. McCANN: We will now proceed with the FDA's introductory remarks from Dr. Sharon Hertz.

FDA Introductory Remarks - Sharon Hertz

DR. HERTZ: Good afternoon, everyone, Dr. McCann, members of the Anesthetic and Analgesic Drug Products Advisory Committee, and invited guests. This afternoon and tomorrow, we will be discussing EXPAREL, bupivacaine liposomal injection suspension. Because the applicant is seeking to change the original indication as well as add a new indication, data will be presented from studies spanning the entire development program.

As evident from the background materials, the applicant and the FDA team disagree about the interpretation of some of the study data, and we have convened this AC to hear your thoughts about the data and your advice about what indications these data support.

When a new formulation of a previously approved drug substance is studied, we generally try to have clinical trials designed to inform prescribers not just about efficacy in a general sense, but to inform prescribers about the differences that result from the new formulation.

So we will often request that applicants include an active comparator in their clinical studies, and we did so in this development program as well, but you'll see that we have a lot of placebo-controlled studies for the pivotal efficacy studies and some additional studies that were active controlled.

To support the request for an indication for nerve block, there were four placebo-controlled phase 3 efficacy studies, two using femoral nerve blocks and one each of interscalene and intercostal nerve blocks. We'll ask you to evaluate whether these studies should support any nerve block indications, and you'll also hear the results of the placebo-controlled and active-controlled studies of EXPAREL when administered by infiltration around the surgical site as these data are helpful for interpreting one of the femoral nerve block studies and also provide the basis for deciding about the proposed change from the original surgical site analgesia indication to the broader local analgesia indication.

Key issues that will be highlighted for

discussion in the questions include what efficacy data are appropriate to support the requested indication for nerve block; if the applicant provided the necessary data; how mixed results from pivotal studies should be interpreted; and similarly, are the available data sufficient to adequately describe important safety considerations.

The use of local anesthetics as part of a multimodal approach to postoperative pain management has become more and more popular particularly as practitioners strive to reduce the use of opioid analgesics. As you consider the available efficacy data, please include your thoughts about what endpoints should be studied for opioid sparing and what comparators are relevant as well, and how this information can be used to be informative to prescribers.

Once again, thank you for taking time from your busy schedules to help us with this advisory committee.

DR. McCANN: 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, the FDA believes that 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 the applicant, such as consulting fees, travel expenses, honoraria, and interest in a sponsor, including equity interest 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 Pacira's presentations.

Applicant Presentation - Michael Rozycki

DR. ROZYCKI: Thank you and good afternoon. My name is Michael Rozycki, and I'm the vice president of regulatory affairs for Pacira Pharmaceuticals. On behalf of all of my colleagues at Pacira, I'd like to thank the committee and the FDA for the opportunity to be here to discuss EXPAREL today.

As you will hear, EXPAREL is an FDA-approved, opioid free, long-acting local anesthetic. Bupivacaine, the active ingredient in EXPAREL, has been widely used for almost 50 years and is a World Health Organization essential medication. Currently, EXPAREL is used more than 3,000 times a day for infiltration and field block to provide safe and effective long-lasting analgesia. Our studies have also shown that EXPAREL can reduce postsurgical use of opioids. We will give you examples of what we have done and what we are planning to do maximize these benefits.

We are here today to present our data supporting the addition of a broad nerve block

indication to the label for EXPAREL. During this presentation, we will also address the specific issues raised by the FDA.

EXPAREL is bupivacaine encapsulated in our DepoFoam drug delivery system. DepoFoam is composed of microscopic, spherical, multivesicular liposomes organized in a honeycomb-like structure. They provide extended release of bupivacaine to give patients longer-acting pain relief.

The liposomal nature of EXPAREL means that the analgesic effect of bupivacaine is localized to the area of administration with little diffusion. This combination of extended release, coupled with the ability to specifically target the desired site of action, is what sets EXPAREL apart from immediate-release local anesthetics.

The FDA approved EXPAREL in 2001 based on two positive, phase 3, randomized, double-blind, placebo-controlled trials. These studies showed efficacy in two representative acute pain models, hemorrhoidectomy and bunionectomy. Because of its demonstrated efficacy for local analgesia, it was

reasonable to expect that EXPAREL would also have utility for regional analgesia, therefore, we conducted two placebo-controlled studies to evaluate the efficacy and safety of EXPAREL when administered as a single-injection nerve block.

Study 322 evaluated intercostal nerve block in patients undergoing thoracotomy and study 323 evaluated femoral nerve block in patients undergoing primary unilateral total knee arthroplasty. These studies were the basis for our supplemental new drug application for nerve block submitted in 2014.

We received a complete response letter in 2015 requesting evidence of efficacy in at least one additional clinical setting. FDA also asked for additional characterization of pharmacokinetics through Tmax and more data regarding the onset and duration of nerve block. And lastly, the FDA requested analyses of existing cardiac safety data.

We resubmitted our sNDA with all of the requested data in October of 2017. Our resubmission included two additional phase 3

trials. Study 326 evaluated femoral nerve block in patients undergoing primary unilateral total knee arthroplasty. Study 327 evaluated brachial plexus nerve block in patients undergoing either total shoulder arthroplasty or rotator cuff repair.

These additional studies and further analyses of existing data have fulfilled the approvability requirements from the complete response letter. As we will show you today, study 327 met the requirement for efficacy in at least one additional setting and was positive for its primary and all secondary endpoints. Study 326 provided the requested pharmacokinetic and sensory motor deficit data.

We included analyses of Holter monitor data from studies 322 and 323 in our sNDA resubmission. As the FDA's briefing document acknowledges, these analyses did not show any evidence of cardiac toxicity with EXPAREL. Therefore, by the criteria set by the FDA in their complete response letter, all approvability issues from the original sNDA are now met.

Our presentation will also address the concerns raised in the FDA's briefing document. First, pharmacokinetic variability. The variability in EXPAREL's PK is influenced by the same factors as all local anesthetics. More importantly, the maximum concentrations with EXPAREL are lower than with immediate-release bupivacaine. Second, we will show how our current clinical data are sufficient to support a broad nerve block indication.

Next, the FDA has raised the question of whether placebo-controlled trials are sufficient for approval. It is important to note that EXPAREL was initially approved seven years ago on the basis of placebo-controlled trials. Similarly, we planned our nerve block development program in consultation with the FDA using placebo-controlled trials.

While we are confident that these trials meet the regulatory requirements for approval, we will also present data from bupivacaine controlled studies to provide clinical context for EXPAREL's

extended pain control. Finally, we will show that EXPAREL has a lower risk of local anesthetic systemic toxicity, or LAST, than immediate-release bupivacaine.

The current EXPAREL indication reads, "EXPAREL is a liposome injection of bupivacaine, an amide local anesthetic indicated for single-dose infiltration, into the surgical site to produce postsurgical analgesia."

Subsequent to the initial labeling, in discussions in 2015, the FDA determined that statements in the EXPAREL label created ambiguity regarding the scope of the indication and that our labeled indication for infiltration encompasses field blocks such as transversus abdominal pain or TAP. This agency clarification is consistent with the way physicians today use EXPAREL across field blocks.

In our new proposed labeling, we're looking to clarify the infiltration statement and to add an indication for nerve block. The proposed indication reads, "EXPAREL is a liposome injection

of bupivacaine, an amide local anesthetic indicated for single-dose infiltration, to produce local analgesia and as a nerve block to produce regional analgesia."

Again, we are proposing the change to the infiltration portion to be more consistent with clinical practice. We will not present data from our infiltration program today since those data were reviewed and approved by the FDA in 2011. Rather, our presentation will focus on our new data that support the proposed nerve block indication. Presently, EXPAREL is only approved for adults age 18 years or older, however, we are working with the FDA on a pediatric development plan.

Here now is the agenda for the rest of our presentation today. Dr. Anoushka Afonso from Memorial Sloan Kettering Cancer Center will discuss the use of local anesthetics and the rationale for using EXPAREL as a nerve block. Drs. Roy Winston and Richard Scranton from Pacira Pharmaceuticals will present our efficacy and safety data, respectively. Dr. Jeff Gadsden from Duke

University School of Medicine will provide his clinical perspective on the results. And then finally, Dr. Scranton will return to conclude the presentation and answer your questions. We also have a number of additional experts with us today to help answer your questions.

Thank you for your attention, and I will now turn the lectern over to Dr. Afonso.

Applicant Presentation - Anoushka Afonso

DR. AFONSO: Good afternoon. My name is Anoushka Afonso. I'm the director of Enhanced Recovery after Surgery at Memorial Sloan Kettering Cancer Center. I'm board certified in both anesthesiology and internal medicine. My goal is to improve both short- and long-term perioperative outcomes for my cancer patients. One of the ways I do that is by providing them with the best possible pain management.

Let me explain how we use local anesthetics in clinical practice, the limitations of our current treatment options, and the rationale for expanding the EXPAREL indication to include nerve

block. Let's start by reviewing the current treatment landscape.

Current consensus guidelines for managing postsurgical acute pain recommend multimodal analgesic regimens. Multimodal analgesia combines two or more agents or techniques that act by different mechanisms to provide better pain relief with fewer opioids and avoid opioid related side effects. Usually this includes the use of systemic analgesics and local anesthetics. Local anesthetics are an obvious choice for postsurgical pain management since they block conduction of pain impulses without systemic side effects.

At my institution, we have developed multimodal analgesic regimens as part of an enhanced recovery after surgery, or ERAS programs, across different surgical subspecialties. As a result of these strategies, our patients have experienced a reduction in opioid consumption as well as length of stay. Local anesthetics are an essential part of these approaches.

Local anesthetics can be used for

infiltration, which is also known as a field block, or they can be used as a nerve block. With both the goal is the same, to block nerves and provide relief from acute pain. In clinical practice, certain procedures are more amenable to one or the other. For example, in a hemorrhoidectomy, a surgeon would infiltrate at the incision site because the pain is more localized. However, in a rotator cuff repair, one might choose to use a single injection nerve block to anesthetize a larger area.

With infiltration, a physician typically uses multiple injections of a local anesthetic under direct visualization around the surgical site. This targets nerve endings only in the surgical field. With a nerve block, a physician can use a single injection to target larger nerves further up the nerve branch usually by ultrasound.

EXPAREL was approved for infiltration and has been safely used for six years. Currently, only conventional local anesthetics such as bupivacaine and lidocaine, are indicated for nerve

block. However, these conventional local anesthetics are limited by a relatively short duration of the action. Most moderate to severe postsurgical pain can last several days, but a nerve block with bupivacaine may last around 12 to 24 hours. Untreated acute pain can lead to chronic pain, so we have to fill in the gap after the nerve block wears off.

There are two options to provide pain relief. One is to insert a catheter to provide a continuous nerve block with local anesthetic directly into the surgical site. The most widely used option, however, is opioids. Both come with their own limitations. The limitations of continuous peripheral nerve block with a catheter and a pump are well documented. For physicians, catheter placement can be technically challenging and take additional time, and many are not comfortable placing them. For patients, potential concerns include catheter migration, infection, or mechanical failure of a pump, and often, patients just don't like going home with catheters.

There's also the issue of exposure. Drug delivery through a catheter can be relatively imprecise and local anesthetic needs to be continuously applied to the nerve. Therefore, patients are commonly administered more than 400 milligrams of local anesthetic per day, but as I mentioned, the only real alternative to a catheter is opioids.

Common adverse events associated with opioids are nausea, vomiting, constipation, ileus, delirium, just to name a few. These invariably lead to increased morbidity, increased hospital stays, and an overall stress on our healthcare system. But the most serious risk of postsurgical opioid use is respiratory depression, and it's alarming how often this happens in hospitals. Studies show that 1 in 83 patients receiving opioids through patient-controlled analgesia, or PCA, after surgery require rescue reversal with naloxone in the hospital.

Finally, a recent CDC study has shown postsurgical opioid use is linked to long-term use.

Approximately 6 percent of patients who receive a prescription for opioids after surgery are still using opioids one year later, and the longer a patient initially uses opioids, the greater the risk. 13.5 percent of patients whose initial use was 8 days or longer were still using opioids one year later. This is why reducing a patient's initial exposure to opioids has been such an important focus in our healthcare system.

To summarize, EXPAREL is an extended-release form of bupivacaine, which is a local anesthetic that has been approved for nearly five decades. EXPAREL has been FDA approved for infiltration and field block since 2011 and has been already used to manage the pain of millions of patients in the United States. Expanding EXPAREL's indication would give us a long-acting, single-shot nerve block, which would reduce total exposure to bupivacaine. EXPAREL would also reduce the need for opioids by providing a viable non-opioid option for our patients.

Thank you for your attention. I will now

invite Dr. Winston to the lectern.

Applicant Presentation - Roy Winston

DR. WINSTON: Thank you, Dr. Afonso, and good morning, or afternoon. My name is Roy Winston, and I am a senior vice president of anesthesia, surgery, and medical affairs at Pacira Pharmaceuticals. I'm a board certified anesthesiologist and have been practicing anesthesia for over 25 years. Previously, I was a lieutenant commander in the United States Navy, served as vice president of the Board of Medical Examiners for the state of Georgia, and was a faculty member at Emory University, University of California Irvine, and Florida State University.

Today, I will present the efficacy data from our clinical development program, which demonstrates that a single administration of EXPAREL as a nerve block provides effective control of post-procedural pain for several days and reduces the use of opioids in the postsurgical setting.

The EXPAREL nerve block program evaluated

representative nerves in the human body. These models included upper and lower extremities as well as a single major nerve and a nerve plexus. Our two positive phase 3 studies support approval of a new, broad, acute pain indication for EXPAREL.

Pacira conducted four phase 3, randomized, controlled, placebo, double-blind, multicenter nerve block studies. Study 327 was a brachial plexus nerve block study in 140 patients undergoing total shoulder arthroplasty or rotator cuff repair. Both doses were initially studied, but the higher dose was dropped based on an administrative decision due to slow enrollment and a recent concluded study showing efficacy of the lower dose in brachial plexus nerve block.

Study 322 was an intercostal nerve block study in 185 patients undergoing thoracotomy. EXPAREL patients received the 266-milligram dose. Study 323 was a femoral nerve block study in 184 patients undergoing primary unilateral total knee arthroplasty. All EXPAREL patients received the 266-milligram dose. Study 326 was another

femoral nerve block study in 230 total knee arthroplasty patients. We evaluated both, the 133- and the 266-milligram doses. Studies 323 and 327 provide the primary efficacy evidence for EXPAREL as a nerve block.

The four studies had similar inclusion criteria. Patients had to be at least 18 years of age and scheduled to undergo the procedure corresponding to each trial. They had to have normal motor function and could not have planned concurrent surgical procedures. Patients could not be on long-acting opioids or NSAIDs within 3 days of surgery and no opioids at all within 24 hours.

In terms of perioperative analgesic medications, preoperatively low-dose aspirin for cardio protection and acetaminophen or paracetamol were permitted before study drug administration. Short-acting opioids were permitted during surgery and specific guidance was provided on the use of rescue medications.

To reflect the current standard of postsurgical multimodal therapy in studies 327 and

326, all subjects received acetaminophen or paracetamol. Following surgery, immediate-release oxycodone was permitted as a rescue medication for pain control. IV morphine or hydromorphone was allowed if oral medications could not be tolerated.

Study 322 used a stepwise approach to rescue, starting with 100 micrograms of IV fentanyl and then either PCA morphine, or hydromorphone, or intramuscular morphine injection. Study 323 also implemented a stepwise approach. First-line rescue was a hydromorphone IV bolus. Second-line rescue was PCA morphine or hydromorphone. Third-line rescue was administration of immediate-release bupivacaine by the previously placed femoral nerve catheter.

The primary endpoint in all studies was the cumulative pain intensity through either 48 or 72 hours. We measured cumulative pain intensity using area under the curve of either a visual analog scale or a numerical ratings scale. The secondary endpoints in the studies were ranked in order of clinical importance. First, total opioid

use, then the percentage of patients who are opioid free, and then finally time to first opioid use. These secondary endpoints were analyzed hierarchically as shown on the slide.

Efficacy analysis included all patients who received the study drug and underwent the planned surgery. For the primary endpoint, we accounted for rescue medication using a conservative approach. In cases when a patient took rescue medication, their pain intensity scores were imputed using the windowed worst observation carried forward method. Pain scores during and after rescue were imputed with the highest pain score for a prespecified duration from the end of surgery until the time of rescue medication. Missing data were handled using either last observation carried forward or multiple imputation depending on what was prespecified in each study.

Now, let's move to the patient demographics. The mean age across the studies was 60 to 65 years and the majority of patients were Caucasian. In studies 327 and 322, approximately two-thirds of

patients were male, while in studies 323 and 326, more than half were female. Patients in studies 327 and 323 were either predominantly or entirely from the United States. Patients in study 322 were almost entirely from outside the United States, and study 326 had an even split between U.S. and non-U.S. patients. Completion rates were generally high across the studies. In each study, reasons for discontinuation were similar across groups.

Now, let's review the efficacy results of each study individually starting with study 327, our brachial plexus nerve block study, in total shoulder arthroplasty and rotator cuff repair. The primary efficacy endpoint was met. The 133-milligram EXPAREL group had significantly lower cumulative pain scores compared to the placebo through 48 hours. This reduction in pain can be seen on the graph, which shows mean VAS scores of approximately 2 to 3 throughout the study for the EXPAREL group and mean VAS scores of 5 to 7 for the placebo group.

Importantly, the reduction in pain was observed in combination with a dramatic reduction in opioid consumption. Through the first 48 hours after surgery, EXPAREL patients consumed less opioid medication than placebo patients. On average, the EXPAREL patients received a total of 12 milligrams compared to 54 milligrams of IV morphine equivalents as compared to placebo. This represents a 78 percent reduction, which is highly statistically significant.

I should also mention that the calculation for opioid consumption shown here and in study 326 has been updated from what you previously were provided in your briefing materials and was only recently provided to the FDA. This update corrects the conversion factor for oral oxycodone to IV morphine equivalent doses and is consistent with the current consensus in the literature. This revision does not affect the conclusions regarding the reduction in opioids with EXPAREL. The percent reduction in fact went from 77 to 78 percent, and the value is still less than 0.0001.

This slide illustrates that significantly more EXPAREL patients remained opioid free through 48 hours postoperatively compared to placebo. Thirteen percent of EXPAREL patients, or about 1 in 8, were opioid free through 48 hours compared to only 1 percent in the placebo group. Total shoulder arthroplasty and rotator cuff repair are known to be very painful postoperatively, so the ability to have any patients opioid free after these surgeries is clinically meaningful.

EXPAREL patients also had a longer time to first use of rescue medication. The median time to opioid rescue was more than 4 hours with EXPAREL and only about 35 minutes with placebo. Overall, study 327 demonstrated that EXPAREL was efficacious for nerve block in an upper extremity while at the same time substantially reducing postoperative opioid use.

Now let's review the results of study 322, our intercostal nerve block study and thoracotomy. The primary efficacy endpoint in study 322 was not met. The cumulative pain intensity scores through

72 hours were similar with both EXPAREL and placebo. After review, it was clear that there were significant limitations that precluded us from interpreting efficacy in this study.

First, the technique did not provide a block for the chest tube site. All patients in both groups had at least 1 chest tube inserted during surgery. Also, in both groups, the mean duration of chest tube use exceeded 90 hours. The pain from a chest tube alone is often overwhelming by itself. Secondly, the technique employed in the study only blocked 3 nerves: the index nerve, one above, one below. For an incision of this length, a minimum of 5 to 7 nerves must be blocked to provide adequate analgesia.

Taken together, the technique used in this study was inadequate for either a thoracotomy incision or a chest tube, and certainly for both. Additionally, the PK data showed that EXPAREL was absorbed and cleared very quickly. This is consistent with a combination of intravascular, intrapleural, and intramuscular injection. A nerve

block was not achieved due to inadequate administration technique. As a result, the efficacy of EXPAREL as a nerve block cannot be meaningfully evaluated in this study.

Turning now to our first femoral nerve block study in total knee arthroplasty patients, in this study, the primary endpoint was met. The mean cumulative pain intensity scores through 72 hours were lower in the EXPAREL 266-milligram group compared to the placebo group. The analgesic benefit of EXPAREL is illustrated here with pain intensity separating between the two groups early and maintained through 72 hours.

As with study 327, EXPAREL patients experienced less pain and consumed fewer opioids compared to placebo. Patients in the EXPAREL group took, on average, a total of 93 milligrams of IV morphine equivalents compared to 122 in the placebo group. This was a statistically significant reduction of 24 percent.

The percentage of patients opioid free through 72 hours was not a ranked secondary

endpoint. All patients in both groups used at least one opioid rescue medication at some time during the study. Time to first opioid use was similar in both groups with a median time of approximately 30 minutes. Overall, study 323 demonstrated that EXPAREL 266 milligrams provided efficacious regional anesthesia in a lower extremity while also reducing the use of opioids.

Next, let's review the results of study 326, an additional femoral nerve block study in patients undergoing total knee arthroplasty that evaluated both the 133- and 266-milligram doses. Unlike study 323, in addition to a femoral nerve block administered by the anesthesiologist, the surgeon performed a periarticular infiltration of the posterior capsule with immediate-release bupivacaine prior to placement of the prosthesis. This was done in both EXPAREL and the placebo group.

Neither of the doses achieved statistical significance for the primary endpoint cumulative pain intensity scores through 72 hours. We

thoroughly evaluated potential factors that may have led to this negative finding. Placebo patients in study 323 did not receive any local anesthetic. In contrast, study 326, all patients, including those in the placebo group, received a posterior capsule injection with 40 milligrams of immediate-release bupivacaine.

This in part may have contributed to the lower pain scores across all groups in study 326. Both EXPAREL and placebo cumulative pain scores were 40 to 46 percent lower in study 326 as compared to study 323. In retrospect, study 326 should have enrolled a larger sample size to account for this smaller expected treatment effect due to both groups receiving additional local anesthesia.

I would now like to present two bupivacaine controlled investigator initiated trials that were included in our submission. These trials provide data on EXPAREL as a nerve block in additional clinical settings. In these trials, EXPAREL was combined with bupivacaine. Both studies were

blinded, randomized, controlled trials in small distal extremity nerves. These were different settings from the single major nerve and nerve plexus studies we reviewed earlier.

In study 1601, 32 patients undergoing Dupuytren's contracture release randomized 1 to 1 to receive a nerve block with either EXPAREL 133 milligrams combined with bupivacaine 25 milligrams or bupivacaine 75 milligrams alone. For both groups, drug administration was performed under ultrasound guidance and with nerve stimulation. This was done to ensure that the anesthetic was deposited in the tissue plane between the superficial and deep flexors of the forearm, targeting the median and ulnar nerves.

All patients received standard multimodal post-procedural analgesia. The efficacy endpoints included the need for additional local anesthetic during finger manipulations, which were done 48 hours after study drug administration. Patient reported worse pain over the first 72 hours and patient reported numbness over the first week.

Forty-eight hours after study drug administration, only 19 percent of patients in the EXPAREL admixed group required additional local anesthetic at the time of contracture release. This compares to 94 percent of patients who received only immediate-release bupivacaine. This was highly statistically significant.

In addition, cumulative worse pain scores were significantly lower for the patients who received the EXPAREL plus bupivacaine than for those who received immediate bupivacaine from day 1 to day 3. Finally, 68 percent and 44 percent of patients treated with EXPAREL plus bupivacaine still had reported numbness at days 3 and 4, respectively. No patients in the immediate-release bupivacaine group had reported numbness after day 1.

Moving now to the next study, study 1602 was conducted in a surgical acute pain model with 40 patients undergoing scarf osteotomy. Patients were randomized equally into three groups: EXPAREL 133 milligrams with bupivacaine 25 milligrams,

bupivacaine 75 milligrams alone, or general anesthesia. Nerve block was performed under ultrasound guidance and with nerve stimulation to target the posterior tibial and deep peroneal nerves.

All groups received standard multimodal post-procedural analgesia. The efficacy endpoints were opioid consumption in the first postoperative week, patient-reported worse pain over the first 72 hours, and patient-reported numbness of the foot over the fourth first postoperative week.

The average opioid consumption during the first postoperative week was significantly lower in subjects who received EXPAREL plus bupivacaine compared to those who received immediate-release bupivacaine alone and those who received general anesthesia as well. Opioid consumption was 64 percent lower for EXPAREL plus bupivacaine than bupivacaine alone and 84 percent lower compared to general anesthesia.

Repeated measures analysis also determined that the pain scores in the EXPAREL admixed group

were significantly lower than those in the general anesthesia group. And consistent with study 1601, patients who received EXPAREL were more likely to have patient-reported numbness. For example, 75 percent of patients still had numbness at postoperative day 3 compared to only 21 percent of patients who received bupivacaine alone and 8 percent who received general anesthesia.

Overall, the results of the investigator initiated trials provide additional support for the efficacy of EXPAREL as a nerve block as well as its potential to substantially reduce patient exposure to opioids in an active comparator trial.

In summary, efficacy of a single administration of EXPAREL as a nerve block was demonstrated for both doses in two adequate, well controlled trials. Our representative models included the brachial plexus located in the upper extremity as well as a single major nerve in the lower extremity. EXPAREL also reduced opioid use by 25 to 75 percent, and in the brachial plexus study, a significant proportion of EXPAREL remained

opioid free.

Efficacy was also demonstrated in two active controlled investigator initiated trials in distal extremity peripheral nerve blocks in both surgical and nonsurgical acute pain. In conclusion, the data demonstrate that EXPAREL is an efficacious, opioid-free, extended-release analgesic, which provides long-lasting pain control with a single administration.

Thank you. I'll now invite Dr. Richard Scranton to review the safety results.

Applicant Presentation - Richard Scranton

DR. SCRANTON: Thank you, Dr. Winston.

My name is Richard Scranton, and I'm the chief scientific officer at Pacira. Previously, I was a lieutenant commander in the United States Navy Medical Corp, and then an assistant professor of medicine in the Department of Aging at the Brigham and Women's Hospital, where I also received my MPH in clinical effectiveness from the Harvard School of Public Health. I will review the safety results supporting the nerve block indication for

EXPAREL. I will start with a brief background on the pharmacokinetics of local anesthetics.

The PK of local anesthetics are not related to the local analgesic efficacy. The analgesia is based on the availability of the anesthetic at the specific anatomic location rather than the systemic concentration of the drug in plasma. This is in contrast to systemic agents like opioids, where the PK is highly correlated with analgesia. While local anesthetic PK is not predictive of efficacy, it is useful for safety. High concentrations of local anesthetics are associated with neurotoxicity such as muscle twitching or seizures and cardiotoxicity such as hypotension or arrhythmia.

Next, I will show an example from head-to-head data with EXPAREL and immediate-release bupivacaine to give you a sense of the PK profiles. These are the results from our phase 2 study of an ankle block and a bunionectomy. They illustrate that EXPAREL is associated with lower maximum concentrations than immediate-release bupivacaine. You can see that the mean concentration for

125 milligrams in gray reaches a Cmax of about 550 nanograms per mL at approximately half an hour. The EXPAREL dosages of 155 and 310 milligrams in blue didn't reach Cmax until 24 to 48 hours after administration.

Importantly, the Cmax for both doses of EXPAREL was considerably lower than that of bupivacaine. This is due to the slow release of bupivacaine, an aspect of our formulation which has been well established in our clinical program for nerve block and infiltration. While other studies show different PK curves, the pattern of the extended release of bupivacaine remains the same.

In the briefing book, FDA identified the variability in EXPAREL's PK profile with different nerve block administration techniques. They stated that the PK profile at sites that have not been evaluated is still unknown and that Pacira has not provided an adequate rationale to support extrapolation of the PK and safety data to other nerve blocks.

We acknowledge that the PK profile of all

local anesthetics for different nerve blocks, including EXPAREL, are influenced by several factors. These include the dose, the vascularity of the administration site, and the administration technique as well as wide interpatient variability. This phenomenon is not unique to EXPAREL. In fact, the current label for marketing, which is immediate-release bupivacaine, acknowledges the variability by these factors.

To quote from the label, "The rate or systemic absorption of local anesthetics is dependent upon the total dose and concentration of the drug administered; the route of administration; the vascularity of the administration site; and the presence of epinephrine in the anesthetic solution."

With that in mind, now I'll turn to the results of our clinical studies. The nerve block safety evaluation consists of six phase 2 and phase 3 studies. The pooled exposures include 531 patients exposed to EXPAREL and 357 exposed to placebo. Study 326 was the only study that had a

randomized comparison between dosages.

Here is the overall summary of adverse events in the pooled analysis. The incidence of adverse events was generally similar between the EXPAREL and placebo groups. Severe adverse events were numerically higher in the 266-milligram group compared to the 133-milligram group, but both were similar to placebo. There were few adverse events leading to discontinuation in any group. The rate of serious adverse events was also similar to placebo, and there were 6 deaths across the entire nerve block clinical program, which I will describe in more detail shortly.

To show the relative difference by dose, we looked at study 326. That was the only study that provided a randomized comparison of the 2 dosages. This is important because pooling across all the nerve block studies and surgeries can confound the relationship between the dosages. In study 326, the rates of all event types were similar to placebo.

Here are the serious adverse events that

occurred in 3 or more patients in the pooled EXPAREL groups. The total number of SAEs was higher in the 266-milligram group because that was the only dose evaluated in the thoracotomy study, which was the most invasive procedure and comprised of the sickest patient population. In study 326, the overall incidence in the EXPAREL groups was similar to placebo.

The most commonly reported preferred terms linked to a serious adverse event were pyrexia, post-procedural hematoma, pneumonia, myocardial infarction, and urinary tract infection. None of the SAEs in any study were considered to be related to study drug. As mentioned, there were 6 deaths in the clinical program. All occurred in the thoracotomy study, 2 in the EXPAREL 266-milligram group and 4 in the placebo group. Most of these events were cardiac in nature and none were assessed to be related to study drug by the investigator.

Next, I'll review the adverse events of special interest starting with local anesthetic

systemic toxicity. Local anesthetic systemic toxicity is a rare, potentially life threatening, rapid onset constellation of CNS and cardiovascular symptoms. For bupivacaine, systemic toxicity can result from plasma concentrations above 2000 nanograms per mL. It may occur quickly when a local anesthetic is inadvertently injected intravascularly or used in excess of the maximum dose. There were no cases of systemic toxicity in our clinical studies.

Pacira also conducted a review of all suspected cases of local anesthetic systemic toxicity in our postmarketing database and in the literature from the time of marketing through May 2017. There were 3 million exposures during this time frame. We identified 63 cases where local anesthetic systemic toxicity could not be ruled out.

Taking a conservative approach where we assume that all of these cases were definitive, the incidence with EXPAREL would be approximately 0.2 cases per 10,000 patients. In contrast, the

reported rate from nerve block with immediate-release local anesthetics is somewhere between 2 to 2.8 cases per 10,000 patients.

Pacira also conducted several preclinical studies in dogs to evaluate the relative PK and safety of an inadvertent intravenous, intra-arterial, epidural, and intrathecal administration of EXPAREL compared to bupivacaine. Let's look at one of these studies, which evaluated the risk of IV administration.

This graph shows mean bupivacaine plasma concentrations over time. Immediate-release bupivacaine administered intravenously at 1.5 milligrams per kilogram was associated with peak plasma concentrations of approximately 2400 nanograms per mL. EXPAREL at 3 times that dose, or 4.5 milligrams per kilogram, had peak levels of approximately 1800 nanograms per mL, still below the range associated with any systemic toxicity. These data suggests that the liposome-bound nature of bupivacaine in EXPAREL may provide an enhanced safety margin against local anesthetic

systemic toxicity compared to immediate-release bupivacaine.

Next, let's turn to falls. The incidence of falls was comparable between the 133-milligram and 266-milligram EXPAREL groups, but both were higher with the EXPAREL than with placebo. All falls among EXPAREL patients occurred in the TKA studies. To minimize the risk of falls and based on the known effects of bupivacaine, we are proposing the precaution for our label that EXPAREL is not recommended for use as a femoral nerve block if early mobilization and ambulation is part of the patient's recovery plan. However, there may be cases when early ambulation is not a clinical goal such as lower extremity trauma, deformity correction, or amputation. In these cases, a long-lasting femoral nerve block with EXPAREL could be clinically appropriate.

Finally, let's review sensory and motor function in studies 326 and 327. In these studies, sensation loss was defined as the absence of sensation of cold, a pin prick, or a light touch.

Motor function was assessed by measuring the change from baseline in knee flexion and extension in study 326 and by evaluating thumb abduction, adduction, and opposition as well as elbow flexion in study 327. In the interest of time, I will only briefly review the sensory function results, but you can find additional assessments in your briefing materials.

In study 326, sensory function was intact at baseline and as expected, patients experienced a loss of function as the nerve block took effect leading up to surgery. Postsurgery, patients regained function as the effect wore off, and there was no evidence of long-term sensory loss. A similar pattern was noted in study 327. Patients experienced sensory loss leading up to surgery and gradually regained function postsurgery.

In summary, the results of the clinical program demonstrate that EXPAREL is safe and well tolerated when administered as a single injection nerve block to produce regional analgesia in various surgical procedures. There were no

clinically meaningful differences in the safety profile of EXPAREL as a nerve block compared with its well established safety profile in infiltration with the exception of falls, which will be addressed with a precaution in the label.

Overall, the data demonstrate that EXPAREL is a safe, long-acting, non-opioid pain management option following surgery or injury. The favorable safety and nerve block is supported by the well known profile in the improved indication and supported by more than 3.5 million patient exposures in the U.S. Thank you for your attention. I'll now turn the lectern to Dr. Jeff Gadsden to provide his clinical perspective on the results.

Applicant Presentation - Jeff Gadsden

DR. GADSDEN: Good afternoon. My name is Jeff Gadsden, and I'm an associate professor and chief of the Division of Orthopaedics, Plastics, and Regional Anesthesia at Duke University Medical Center. I'm also the director of the Regional Anesthesiology and Acute Pain Medicine Fellowship

at Duke, and I'm here today to provide my clinical perspective on EXPAREL and the FDA questions.

Since it was introduced in 2011, I've used EXPAREL about a thousand times in my practice, both as infiltration and as a nerve block. Back in that time, we were already beginning to see the failure of the paradigm that we learn in medical school; that's don't leave a patient in pain, use opioids, they won't get addicted if they're really in pain, and clearly that wasn't true in every case. At the same time, we were acutely aware of the limitations of using traditional local anesthetics for nerve blocks.

So take a common procedure like shoulder surgery, for example. If you give a patient a single injection nerve block with bupivacaine or ropivacaine, the patient would feel great in the recovery room, but they'd wake up at home at 2:00 in the morning in pain with no resources other than to take an opioid. These types of experiences have led me to look hard at adjuncts to provide long-lasting pain relief for my patients while also

minimizing opioids, and one of these has been EXPAREL.

So today I want to provide my perspective on three key points related to EXPAREL's benefit-risk profile. First, the sponsor's clinical data and my own experience give me assurance that EXPAREL is safe for nerve block. Second, the clinical trials demonstrate that EXPAREL provides long-lasting pain relief and also that these results can be applied across a wide range of nerve blocks. And finally, EXPAREL has the potential to meaningfully impact healthcare utilization and reducing our reliance on opioids in clinical practice.

I'll elaborate on each of these points, and I'll start with safety. When we consider safety, we have to remember that we've been using immediate-release plain bupivacaine for infiltration and nerve block for decades. Reflecting on my own experience, there are few nerves in the body where I haven't used bupivacaine. EXPAREL is extended-release bupivacaine. It's the same molecule encapsulated

in a slow-release form. In terms of how the molecule interacts with the nerve fiber, EXPAREL behaves in exactly the same manner as immediate-release bupivacaine.

Consistent preclinical, clinical, and postmarketing data all point to EXPAREL being safe for nerve block. In fact, pharmacokinetic data suggests it's safer than bupivacaine. So remember, to sustain a nerve block, as has been discussed already, with an immediate-release local anesthetic, you have to put in a nerve catheter and continuously infuse drug over several days, and sometimes as much as 4[00] to 500 milligrams of local anesthetic is used every day in these techniques.

A single shot of EXPAREL on the other hand will effectively block pain for several days substantially reducing patient exposure to drug. EXPAREL also has a lower risk than immediate-release bupivacaine for the most serious nerve block related complication. That's local anesthetic systemic toxicity, or LAST.

Because bupivacaine is encapsulated in DepoFoam, EXPAREL provides an additional safeguard against these serious events by slowly releasing over time. The preclinical data show that even if an entire dose of EXPAREL is administered intravascularly by mistake, blood levels will not get anywhere a toxic dose of bupivacaine.

These data and the mechanism of action give me great comfort as a clinician that I don't have every time when I'm using immediate-release bupivacaine. So while PK is a guide for me for safety, I want to emphasize that we don't use PK to evaluate efficacy or guide dosing of local anesthetics. The factors influencing EXPAREL dosing are well understood. They're the same as for all local anesthetics. The dose depends on the size and the region of the area being treated, the vascularity of the tissue, and the physical condition of the patient as well as the duration of analgesic required.

As an anesthesiologist, these are the parameters I use when dosing each individual

patient every time, not PK. I also want to emphasize the variability in Tmax is both expected because of the variations in tissue vascularity and at the same time is inconsequential to my clinical decision-making because what I'm really concerned about is a high Cmax because that's what causes LAST.

Another point I want to make is that the clinical results are applicable across a wide range of nerve blocks, and this is important because it's simply not practical to study a local anesthetic in every clinical setting where it may be used. The sponsor has demonstrated efficacy in representative nerve blocks. Brachial plexus is a collection of smaller nerves in the upper limb, and the femoral nerve is a single large nerve in the lower limb. But let me explain why the brachial plexus study in particular makes me comfortable applying the safety and efficacy results to any nerve block.

Study 327 demonstrated efficacy at the interscalene brachial plexus, and that's pictured here. EXPAREL in this block is placed around the

collection of nerve trunks that are in close proximity to multiple vessels in the neck, the spinal cord, the pleura, and other at-risk structures. So if I can do this safely and effectively in the interscalene space with all of these potential pitfalls, I have confidence that I can also use EXPAREL in the same way in any other nerve or plexus in the body.

Finally, I'd like to talk about how using EXPAREL for nerve block could have a meaningful impact on clinical practice. With therapies such a EXPAREL, we are achieving improved healthcare utilization through earlier ambulation in our patients and earlier achievement of physical therapy milestones since patients aren't tide to a catheter and a PCA pump. And with reduced opioid use, we're also seeing less nausea and vomiting and earlier return to bowel function.

Since EXPAREL has been approved for seven years, we also have a number of publications that show that pain relief of EXPAREL can reduce opioid use and length of hospital stay. This slide I'm

showing here shows six examples of studies from well regarded surgical institutions that compare EXPAREL against standard of care, including good old-fashioned, immediate-release bupivacaine. And it's reassuring to me as a practicing clinician to see that independent studies are able to replicate that EXPAREL reduces opioid use, which in turn helps drive down hospital length of stay.

To summarize, I do believe opioid is safe and effective as a nerve block. You've heard today that shorter-acting local anesthetics wear off after about 12 to 24 hours, and our only options to prolong analgesia for moderate to severe pain are to put in a nerve catheter, which is often not feasible or desirable, or to put the patient on opioids. In contrast, a single injection of EXPAREL gives patients sustained, reliable relief for 2 to 3, sometimes up to 5 days.

I have used EXPAREL as a nerve block for lower limb amputations, for ankle fracture, for total knee replacements, for breast cancer surgery. And in my experience, EXPAREL consistently reduces,

and in some cases eliminates, the need for opioids or for additional injections or infusions of local anesthetics. EXPAREL is one part of a multimodal strategy to manage pain while reducing opioid use. It already has a place in our toolbox for field block, and I am convinced by the data showing that EXPAREL will provide substantial benefits as a nerve block.

Thank you for your opportunity to share my thoughts. I'll now turn the lectern back over to Dr. Scranton.

Applicant Presentation - Richard Scranton

DR. SCRANTON: Thank you, Dr. Gadsden.

I'd like to conclude our presentation by sharing our actions to address each of the key concerns from the FDA's complete response letter and their briefing document for this meeting. I'll also review our plan for postmarketing activities to maximize the benefit of reduction in opioids with EXPAREL.

Our sNDA has addressed each of the FDA's requests from their CRL. As shown earlier, we

provided a second positive phase 3 controlled study in an additional setting. Our two new phase 3 studies collected additional PK data through Tmax and provided onset and duration data. We also provided extensive cardiac safety analyses for our two initial nerve block studies, which showed no evidence of cardiac toxicity. Therefore, we have addressed each of the CRL concerns.

We have also shown data to address the FDA's primary concerns from their briefing book. Regarding EXPAREL PK, local anesthetic PK levels are only associated with safety events and only at very high concentrations. The maximum concentrations with EXPAREL are lower than that with immediate-release bupivacaine, and variability occurs with all local anesthetics as a function of factors like dose, vascularity, and administration site.

We also showed data to support a broad nerve block indication. EXPAREL's active ingredient bupivacaine has been used for nerve block in the U.S. since the early 1970s. Our extended-release

formulation was shown to be safe and efficacious in two nerve block models, which are representative of the types of blocks being performed in the U.S. today.

With regard to the appropriateness of the comparator, our pivotal studies were placebo controlled to demonstrate the safety and efficacy of EXPAREL for regulatory approval. We've also submitted data from two investigator initiated trials with immediate-release bupivacaine comparator arms. There are also many peer-reviewed publications that provide additional support for the clinical benefit of EXPAREL as an extended-release local anesthetic.

Finally, local anesthetic systemic toxicity is a rare event that can occur with all local anesthetics, including EXPAREL. However, our postmarketing data and preclinical animal studies suggest that EXPAREL's extended-release properties provide an additional margin of safety compared to immediate-release bupivacaine.

Next, I'd like to discuss our phase 4 plans

and partnerships with hospital systems, payers, and professional societies to realize the full potential of EXPAREL to reduce opioid use. Now that we've shown that EXPAREL can reduce opioid use in the acute care setting, we need to translate that into reducing opioid prescribing after procedures because we won't achieve the intended public health benefit if patients are still walking out of the hospital with an opioid prescription, even when they're not in pain.

To make a meaningful difference, we have to change prescribing behaviors. Let me tell you what we've already done as well as our plans to help fully realize the benefits of a long-acting, non-opioid anesthetic. Pacira is partnering with institutions who share our passion for being part of the solution to manage pain while minimizing opioid use. Here are some of the key partnerships we've already begun. These include programs to educate providers and patients and strategies to minimize the use of opioids.

We are committed also to assessing the

impact of these initiatives. To that end, we are conducting clinical effectiveness studies to evaluate the impact of EXPAREL on opioid prescribing in a real-world setting. One example is an ongoing study with the American Association of Oral and Maxillofacial Surgeons and Aetna to reduce opioid prescribing after wisdom teeth extraction, which for many young adults is their first exposure to opioids.

Pacira's role will be to train oral surgeons on the appropriate use of EXPAREL and the need to reduce opioids, and Aetna will evaluate the program's success. We are also implementing other large scale initiatives to minimize the acute and potentially chronic consequences associated with excessive opioid use.

To summarize, Pacira has provided data that addresses the key concerns from the complete response letter and the FDA briefing book. We are proposing two changes to our currently approved indication. First, a revision to our indication for infiltration to align the label with how local

anesthetics are used as a field block in clinical practice. Second, we are proposing adding an indication for nerve block supported by the safety and efficacy data presented here today.

Our clinical studies have also shown that the long-lasting pain relief achieved with EXPAREL can substantially reduce opioid use after surgery. And finally, we are committed to conducting postmarket studies and advancing partnerships with other organizations to maximize the benefits of opioid reduction with EXPAREL.

Thank you for your attention. We'll now take your questions.

Clarifying Questions

DR. McCANN: Are there any clarifying questions for Pacira? Please remember to state your name for the record before you speak. If you can, please direct questions to the specific presenter. I actually have a question.

DR. SCRANTON: Yes, Dr. McCann?

DR. McCANN: Where do the liposomes come from, and what is their effect when they're

injected intravascularly? Are they allergenic? Do they cause emboli if they're injected intra-arterially?

DR. SCRANTON: Yes. The liposomes that we retrieve, they're naturally occurring liposomes. We've studied the lipid components extensively in various animal studies to see if there was any inflammation or reaction, and we've not observed any of that. We can bring up a picture of the actual multivesicular liposome that demonstrates the size. In our studies, when we did our animal studies and our intravascular and intra-arterial, it's a very small micron.

Can we bring up -- there we go. Just to give you an idea what they look like, they're very small, but because of that multivesicular liposome component, 25 microns is the average size. We did not see any evidence of embolic event when we did dissection of our animal models in either spleen or in the lungs.

DR. McCANN: When you said naturally occurring, what does that mean?

DR. SCRANTON: We obtain these from various sources. I can get you the actual components of each one of the liposomes and where they come from. We've been using this for about 20 years, but I can get that for you after the break, where they're all broken up and where they're achieved from.

DR. McCANN: Thank you. Dr. Higgins, please?

DR. HIGGINS: I have a couple of questions about the adverse events. The first is for Dr. Scranton. Was there any correlation found between falls and age?

DR. SCRANTON: Yes. Thank you. In the TK studies, we did observe falls, and the average age there was 65.

If we could bring up the summary slide of the individuals who had falls. You can see here the age of individuals who did have falls. On the 133, the lower dose, 55; 67, and 266. Again, the average age in this population having total knees is around 65. It's important, there was no clinical sequelae from any of these individuals who

did have a fall.

DR. HIGGINS: My second question is for Dr. Gadsden. My understanding is that the way this works, EXPAREL is to create a numbness, a lasting sort of numbness effect, to block pain. But you state that the EXPAREL block actually facilitates earlier PT milestones. How is this possible that the two exist?

DR. GADSDEN: Jeff Gadsden from Duke. The meaning of my statement there simply relates to the fact that if patients have less pain, they're able to get out of bed earlier and walk around, do their stairs, do their bending over touch their toes test compared to patients that are wincing every time they have to bend over. And many of our patients that are achieving these milestones are receiving fascial plane blocks or field blocks with EXPAREL in the TAP block or quadratus lumborum block areas, and they get a numb abdomen for about 2 to 3 to 4 days compared to the patients that have to rely on intermittent opioids. And in those analgesic gaps that they have between opioid doses, they're

experiencing pain and are unable to get out and do those things.

DR. HIGGINS: So the numbness is not felt in the extremities then? Am I understanding that?

DR. GADSDEN: Thank you. It all depends on where you put the local anesthetic. If our patients are getting an ankle fracture surgery, for example, and you put the local anesthetic in the popliteal sciatic nerve area, they'll get a very numb foot and ankle, which allows you to, again, get out and do your crutch walking with a little less discomfort than if you had to rely on the intermittent opioid therapy.

DR. HIGGINS: Thank you both.

DR. McCANN: Dr. Litman, please?

DR. LITMAN: Thank you. A couple of follow-up questions on the other panelists. Dr. McCann was asking about toxicity in the tissues, but you weren't clear on whether or not that was intravenous. The way I think about nerve blocks, if you could do a general infiltration, you're far less likely to get it inside a vein or

artery than you are as if you're targeting a specific nerve, which often runs next to the vessels.

Have you ever taken animals and actually injected this into their veins and arteries and then --

DR. SCRANTON: Yes. We can bring up the animal study. In discussion with the FDA, we did conduct those because, absolutely, the concern was moving the nerve block, that there is a risk for inadvertent intravascular injection. This was in a dog study where we were doing that administration, and the dose at 4.5 milligrams in blue, you can see that that line reaching that peak concentration is still way below the 2,000 level at 3 times the dose.

DR. LITMAN: Right, but that's not what I meant; I didn't mean the PK. I meant the actual tissue damage.

DR. SCRANTON: Tissue damage at the --

DR. LITMAN: Yes, because you're getting theoretically some enhanced concentration somewhere

else. I don't know, maybe one of the organs. Was there anything like that looked at?

DR. SCRANTON: With regards to an intravascular injection, when we did look at those small animal studies, we couldn't find where the drug is depoting. It appears, to your point, about 30 percent is released, and the rest of the DepoFoam is being DepoFoamed [ph] probably along the capillary beds and then slowly being released. And we couldn't identify where that was or if there was any toxicity.

Is there a question with regard to toxicity at the local infiltration site, though?

DR. LITMAN: No. That's what I was -- so the next follow-up question is, Ms. Higgins, she asked about the falls. How did those compare with, say, a bupivacaine group? Was there any difference?

DR. SCRANTON: In the two TK studies, we didn't have active comparator in those particular studies, but when you look from the literature, there had been a significant report of falls,

particularly with continuous nerve block catheter for femoral, and many individuals had been moving away from using continuous nerve block. But the report from the literature that's been reporting for falls are similar to what we would observe from a continuous nerve block from what we observed in that study.

DR. LITMAN: One last follow-up question for Dr. Winston. On the knee study, it didn't specifically say it, but I assume you did not use ultrasound to get the femoral block because you said it in the other studies.

DR. WINSTON: Dr. Winston from Pacira Pharmaceuticals. For the knee studies, we did in fact use ultrasound for placement of the nerve block, yes.

DR. LITMAN: I was just curious. The statistics were significantly different but the results weren't that impressive. Was it because you just didn't do a sciatic?

DR. WINSTON: I think that's part of the challenge, is that getting the femoral nerve

doesn't anesthetize the entire field. And I think these days people have evolved pretty much to doing let's say adductor canal and iPACK instead of femoral nerve for TKA. So I think the marketplace has evolved.

DR. LITMAN: Thanks very much.

DR. McCANN: Dr. Shoben?

DR. SHOBEN: I think all of my questions are for Dr. Winston. The first one was about the demographics of the patients in the clinical trials, and I noticed you didn't include BMI. Is there a reason for that and do you have that data?

DR. WINSTON: I think we do have the BMI data. If I could compile it and get it back to you after the break.

DR. SHOBEN: Sure. And more generally, you stated that the missing data -- if they used the rescue medication, you imputed the pain scores, and you used the worst within a window, and then you claimed that that was conservative. Can you explain why that would be necessarily conservative in all circumstances?

DR. WINSTON: I can, but what I'd like to do, if possible, is have my biostatistician, Dr. Conner, handle that.

DR. CONNER: Hi. I'm Jason Conner from ConfluenceStat and also an associate professor of medical education at the University of Central Florida College of Medicine. I'm a paid consultant to Pacira, but I have no stake in the company nor in the outcome of this meeting or the drug's approval.

This plot shows what is happening. There are two types of imputation. You mentioned in particular when a rescue medication was used. So imagine this is a representative patient. The patient has a pain score of 6, for instance at 6 hours, and that triggers a window that's dependent upon the drug use. For instance, if it's oxycodone, that's a 6-hour window. Any scheduled pain score from then on carries that one value forward because you can see if a patient gets oxycodone, for instance, their pain is expected to go down. We know that works well. So that carries

forward and is used to impute throughout there.

We also have the primary outcome done using just the raw scores, and we can show that to you if you want. It would be PE-14. This was the shoulder study. These values are lower. When we impute the data initially, they're higher. This shows the effect size is about the same, still highly statistically significant. And the key is that there was dramatically lower opioid use with EXPAREL, and even without using the imputation, just using raw pain scores, we still see this big difference in pain between groups.

DR. SHOBEN: My only point would be that I wouldn't necessarily characterize that as conservative imputation because there is a difference between the groups in terms of the rescue medication used, and you're imputing higher pain scores for the group that's using more rescue medication.

DR. WINSTON: Agree. And it turns out that actually in the 326 failed study, the differences get bigger between groups, we didn't see much of a

difference, and when we use just raw scores, we actually start to see a separation.

DR. SHOBEN: Thank you.

DR. McCANN: Dr. Zacharoff.

DR. ZACHAROFF: Hi. This first question I believe is for Dr. Scranton referring to slide CO-77, which talks about proposed precaution for femoral nerve block. It says, "Precaution in label when you use femoral nerve block of early mobilization and ambulation as part of a patient's recovery plan," but yet it seems that that tends to contradict some of the conclusions at the end of the presentation with respect to shorter hospital stays, early ambulation, and so on and so forth. So I'm wondering how this fits into what the plan is.

DR. SCRANTON: Thank you. First, for femoral nerve block, I guess the best way to provide that example is we've actually moved away from a femoral nerve block for a TKA because across this country, the goal is really to get patients up on day of surgery, and then we're actually moving

now to where we actually do same-day TKA. And we're able to achieve that by not doing a femoral nerve block, but actually by doing a periarticular infiltration.

This is an example of a phase 4 study that we did with EXPAREL compared against bupivacaine where we did a periarticular. Now we can cover -- I just want to be clear. When we're doing a femoral nerve block, we're only covering the anterior part of the knee. The posterior part of the knee is not being covered, and patients do experience pain from that, and if they experience pain in this country, they will get opioids.

So here we're covering the entire pain that these patients experience, and we're able to get these patients up and ambulating on day of the surgery. This is a very tight protocol. You had to have PT on the day of the surgery, and we did PT every 12 hours because as the bupivacaine was wearing off, our expectation would be they would take more opioids. And that's indeed what we observed in this study, a significant reduction, a

78 percent reduction in opioids.

This was particularly beneficial in individuals over the age of 65. Getting those individuals up and ambulating soon was very beneficial, and we did see time to discharge readiness being met. But now as you demonstrate those outcomes, now you have to change the system to now allow patients to go home sooner. And that's why now you'll see us moving towards, where appropriate, same-day surgeries for TKA. Femoral nerve block in that setting probably would not be the appropriate way to achieve pain in that individual.

DR. ZACHAROFF: One more question for Dr. Gadsden, I believe, with respect to the comment of sustained pain relief for 2 to 5 days. I think you talked about numbness as well, and I'm wondering is there any concern about the fact that the patient might have numbness for that period of time. Sometimes that's not necessarily a good thing.

DR. GADSDEN: Agreed. This becomes a

concern for us whenever we prescribe local anesthetics, especially a long-acting continuous infusion of local anesthetics via a catheter. A good example is our total ankle replacement population. We're sending them home. They stay in the hospital for one day with a catheter, two catheters in fact, then they go home for 2 or 3 days with that catheter. So they're getting about 4 days of, as you say, numbness and motor block. That's where clinical judgment, patient selection, and patient education come into the picture, and I would apply those same standards of care to my EXPAREL patients as I would with my continuous catheter patients.

DR. ZACHAROFF: So if the patient were given this medication, sent home, there was concern about development of a compartment syndrome, for example, how would you educate the patient and the family once they're home if they're not going to necessarily be able to feel some of the signs that they might if that were taking place?

DR. GADSDEN: Yes, good question. And we

have many centers -- not just ours, but everybody who sends patients home with these types of catheters and nerve block is obligated to do a good job with education and provide patients with resources through which to get back to the clinicians and report some adverse events or funny feelings and that sort of things.

As an example, in our center, we have a comprehensive education program before the patients go home: this is what to expect; this is what to do; if you have concerns, here's a number to call; and here's a backup number to call. And we apply those, as I said, same standards to our EXPAREL patients.

DR. McCANN: Dr. Terman?

DR. TERMAN: Thank you. I guess this will probably be for Dr. Winston about efficacy. I certainly found study 327 to be pretty powerful, but I noticed that the blocks included interscalene and supraclavicular blocks, and I also noticed that the surgeries included total shoulders and rotator cuff repairs.

Given the difference that you're seeing, for instance between the brachial plexus blocks and the femoral blocks, I wonder if you differentiated the two blocks in the brachial plexus study given also the literature, Kim et al., for instance this fall, where pain or at least opiate use after shoulder surgery is not always the same for all shoulder surgeries. I wonder if you took out or looked independently at the different surgeries as well as the different blocks.

DR. WINSTON: I think I have the data here -- let me put the slide up -- looking at the number of rotator cuff repairs and total shoulder arthroplasty in both the EXPAREL and the placebo groups, and they were fairly evenly distributed, actually a little more of the total shoulder, which I would characterize as a more painful surgery in the EXPAREL group.

With regard to intrascalene versus supraclavicular block, I believe we actually only had one supraclavicular block in the whole series. And I can confirm that for you after the break, but

I'm pretty sure the number was one. We included that thinking that might help enrollment with certain centers and certain individuals. It turned out not to be a factor. We did have it be total shoulder and rotator cuff repair again for enrollment really to include those because I think making it just total shoulder, the sample size starts to go down as far as available patients to enroll, and that was one of our concerns.

Does that answer your question?

DR. TERMAN: I think so, yes. Can I ask one more, though?

DR. WINSTON: Sure.

DR. TERMAN: It still may be you. For 322, with the intercostal blocks, one of the things that you suggested was it probably wouldn't work because there were only 3 levels done if you needed maybe 6 or 7 levels to get it done.

Is that concerning at all given the figure 6 in the FDA briefing document that shows a pretty high intercostal blood level already? And you talk about several reasons why that may take place, but

if it is approved for all blocks, how are we going to make sure that well meaning people don't do 6 or 7 levels and get twice this level in their blood?

DR. WINSTON: That's a good question. I actually am glad you've asked me this to clarify it. I think I have the slide here of the PK levels by vascularity. The dose does not change for the number of levels. The way that you would cover those more levels would be to the dilute the drug further and expand it with saline. So it would be the same 266 milligrams whether you're blocking 3 segments or some surgeons even block 8 or 9. So it's really the exact same dose.

The PK profile shouldn't change based on the number of segments blocked. It's just going to be effective by the total dose. That's why we have that as our limiting dose 266 milligrams for any of that. If you look at the PK profile there -- and we all I think know as anesthesiologists that intercostal is always associated with very high -- any local anesthetic absorption, so we do see that.

DR. TERMAN: I certainly don't disagree that it might not. There's no data, but in fact you're dealing with 6 or 7 arteries instead of 3 arteries, so I think it's still open to debate as to whether it would go up higher or not.

DR. WINSTON: I can also call Dr. Rice. He's a thoracic surgeon that works with this on a daily basis and have him give a little bit of clarity on that.

DR. RICE: Hello. I'm David Rice. I'm a thoracic surgeon and professor of surgery at the University of Texas, MD Anderson Cancer Center. I have been using EXPAREL since 2012 when it became our formulary at our institution. In our practice, it is now currently our favorite method of providing regional analgesia for patients undergoing thoracic surgery.

As you know, thoracotomies are extensive procedures. They're probably one of the more painful procedures that one does. And in addition, they're also associated with, more than any other surgical site, an increased incidence of opioid

utilization, both short term as well as long term out of the 180 days.

Regarding the utilization of EXPAREL for thoracotomies or for minimally invasive thoracic surgery, we have been using a technique that differs quite substantially from the method that was present in the study quoted, 322 I think it was, in that we do a posterior intercostal nerve blockade with slightly expanded EXPAREL. We expand it 50 percent, and we block routinely 5 or 6 intercostal spaces.

We've been doing this routinely since 2012. We have data on over a thousand patients at this point. We have analyzed our data compared to patients who have undergone epidurals and find no difference in cardiac or neurologic toxicity. When we look at pain scores in patients matched for extent of lung resection, extent of surgery, we find actually similar or better pain control in groups that have had the EXPAREL and significant reductions in morphine milligram equivalents, like to the order of 90 percent reduction in MMEs. So

we have not noticed toxicity.

I think one of the issues that we see in the 322 study -- there are a number of them -- there are about seven things that we do different. One is the timing. The timing of injection is important. You saw from some of the other data presented that you don't get your optimal concentration for at least 45 minutes to an hour after injection. We always inject before the thoracotomy incision.

In 322, they were injecting at the end of the case. Additionally, there was no expansion. Early in our clinical experience, we used straight EXPAREL without dilution. We found that when we diluted it and increased the volume of distribution, we got much, much better and much more reliable pain control. There was no expansion in the 322 study.

The numbers of ribs blocked, 3 versus 5, and in fact some people block even up to 8 or 9 interspaces with that event, and then chest drains as well. I think in that study, there was poor

standardization of chest tube placement. By blocking more interspaces, it's far more likely that you're going to block the chest tube, and we always infiltrate in and around the chest tube site. So there are multiple reasons I think why the 322 doesn't reflect what we see in clinical practice.

DR. McCANN: Dr. Gulur?

DR. GULUR: Thank you, Dr. McCann.

Dr. Rice, if you don't mind, I might as well finish asking you since you're here. Have you published this data in peer-reviewed literature?

DR. RICE: We published our initial experience, which was 54 patients that were matched to 54 controls who had epidural, and we showed in the thoracotomy group better pain control in the liposomal bupivacaine group as well as lower opioid. That's been published. We've since expanded our series. We now have 246 matched pairs that we are preparing a manuscript for right now.

I will throw out a caveat that this is part of a multimodal analgesia regimen. This is not

just pure EXPAREL that's doing all of this because we are also combining it with other non-narcotic methods of pain control such as gabapentinoids, IV, acetaminophen, ketorolac, et cetera. In addition, we have a fairly liberal utilization of tramadol, which we don't -- I know it's a weak opioid, but it is exceedingly low addictive potential, so we use that quite a bit as well. But the manuscript should be forthcoming.

DR. GULUR: And is that comparative data that you have? Is your epidural population receiving the same multimodal regimen?

DR. RICE: Not to the same degree because we changed our practice almost uniformly as a group in 2015. So we analyzed the first 123 patients since all 9 of us thoracic surgeons started to do this in this particular way, then we went back in time over the preceding two-year period and took patients who were not managed on the enhanced recovery pathway and compared the results. So many of them, I would say probably 60 percent of the epidural patients, also received ketorolac, whereas it's almost

100 percent of the patients who have been managed with enhanced recovery pathway, which includes the liposomal block. I have these data. If anyone wants to see them in advance of publishing, I'd be happy to share them.

DR. GULUR: Thank you, Dr. Rice.

My other question is for anyone who's responding in terms of safety. I share the question asked about the intercostal, and it's good to hear that it has been used for 6 or 7, but we don't have PK studies from that. The other concern I have from the safety data, question I have, is brachial plexus block. It was mentioned that 133 was the lower dose studied in that and that the higher was not further looked at because efficacy -- you had enough pain control with 133. But were more PK studies done with that population or from a safety signal standpoint?

DR. RICE: Yes. First, we did have PK samples from the intercostal study, and we also thoroughly assessed them for CNS or cardiotoxicity, and we observed no signs or symptoms of

cardiotoxicity or CNS toxicity.

In the 327, with our agreement with the FDA, we did follow the PK throughout the Tmax for both dosages. I can show you those levels. What we've seen consistently with EXPAREL is a linear relationship to dose and Cmax. Here you're seeing that represented here, where in the light blue is the lower dose, 133 milligrams, and then as you use the higher dose, 266, you'll see a higher Cmax. This is what we've seen consistently across all of our administration sites, for example, in the femoral nerve block, where we have comparison on both dosages as well.

DR. GULUR: Thank you. My other question is regarding concurrent use of other local anesthetics, especially infusions in the setting of EXPAREL being administered. Is that something that has been looked at? Given the focus on multimodal, it's not uncommon these days for patients to get IV lidocaine infusions, in fact, for EXPAREL to be used when an epidural has also been placed. Has the company looked at that, and do you have any

data on safety of concurrent use?

DR. RICE: The IV lidocaine, at least in my experience, is a newer phenomenon where we haven't done those co-administration studies with IV lidocaine. There have been case studies and case reports of epidural administration following a TAP block that was done out of Balboa Naval Medical Center. I'm familiar with that case in which they did obtain a PK level after that and was still well below the level of toxicity. From the wound infiltration, I'm also aware of individuals where they've used twice the dose as well as co-administrations of bupivacaine. That was by Springer, published those results. Those levels were also well below the level of 1,000.

So those are the data I'm aware of that are out there. A lot of them are being done independent of us based on the variations of clinical practice.

DR. GULUR: From a safety standpoint, would you feel that would be important given that -- or will there be guidance given on what can be done in

terms of concurrency if the indication was expanded to all nerve blocks?

DR. RICE: Yes. Our recommendation, what's current in the label now for infiltration for admixing, is not to exceed a dose of greater than 50 percent if admixed, and this is how it's been used for the majority of patients who require additional local anesthetic. They will admix with this recommendation here. This is part of our overall surveillance in those 3 million individuals and would comprise individuals who had this.

There have been numerous publications done where admixing has been part of their study as well as active comparators, and Dr. Gadsden can speak to how they're using this in his practice with admixing where appropriate.

DR. GULUR: I'd just like to clarify I wasn't asking about admixing but concurrent use of other infusions of local anesthetics.

DR. RICE: The only other that I have -- most are not using concomitant epidural. There may have been a spinal and then EXPAREL use,

but what we have is just from the literature where it's been published concomitant use. We have studied concomitant epidural for IV lidocaine combination with our dose.

DR. GULUR: Would that be something that would be indicated in the label as far as safety?

DR. RICE: According to our label currently, it's recommended that no additional agents, local anesthetics, be used after administration other than EXPAREL. That's how our current label has been used for wound infiltration, and we would recommend the same for nerve block.

DR. GULUR: Thank you. I have one more question if it's possible. This is regarding healthcare outcomes and utilization outcomes, which has been stressed immensely, opioid sparing in health care, lengths of stay. There are many initiatives, as you can see, with enhanced recovery. We have shown that we can get patients out really, really fast. But the outcomes of interest now in these healthcare utilization studies are really more focused on readmissions,

emergency room visits, et cetera.

Were those studied in your studies purporting that healthcare utilization will be approved per se?

DR. RICE: In the wound and foot infiltration studies, we've conducted large claims database studies where we have not seen an increased readmission rate, and some of those studies have been published. There is probably to date over 450 publications and over 250,000 patients that have been studied, a lot of those in those observational studies.

I can bring up here -- just to give you a summary of all the comparator studies going on. And you're right, there are a lot of different comparators, whether it's an epidural or PCA, and there are different outcomes based on the surgical procedure. But this gives you the depth and breadth of the types of studies being done, and I know from the majority of these studies, we're still at a low incidence of readmission rate, but we're not seeing any increase readmission rate,

even upon earlier discharge, at least from the observational studies that I've reviewed.

DR. GULUR: So you haven't seen an improvement, though, in readmission rates or in longer term outcomes?

DR. RICE: I have not seen -- not that I recall in the studies that they've noted a difference, an improvement in readmission rates.

DR. GULUR: Towards that same point, opioid sparing has been brought up. And we talk about opioid sparing, sparing opioids. During the short inpatient stay, for instance, relatively now in literature it has been shown not to have enough effect on longer term effects.

Dr. Afonso, you had mentioned the persistent postoperative opioid use study where 6 percent of patients do it. That study, if I'm not mistaken, also stated that it was not surgical pain but patient level factors that influenced persistent opioid use. How would you feel that EXPAREL could affect patient level indicators such as behavioral issues, and also the fact that in these studies,

the opioid tolerant patients who were also shown to have more persistent opioid use were actually excluded in your studies?

DR. AFONSO: Anoushka Afonso, Memorial Sloan Kettering, anesthesiology. In answer to your first question in terms of how do we know which patients are going to go on to chronic pain, first of all, I think we're really looking at the acute opioid exposure. There is a paucity of data that still needs to be done in terms of looking at long-term outcomes, what happens when the patient goes from inpatient to outpatient, and that still needs to be done.

However, we do have some data in terms of especially the breast cancer patient population, that those who have uncontrolled acute pain, as many as 20 to 40, as high as 60 percent of those develop into chronic pain, and that's an issue. So really, whatever we can do in terms of controlling their pain postsurgically, especially after surgery, using a long-lasting block would be helpful.

DR. GULUR: No, I agree. I guess my question was that one of the outcomes being expressed is that EXPAREL would be opioid sparing. I agree with the pain control, absolutely, but what's the benefit of EXPAREL in this in terms of improving these longer term outcomes, on being truly opioid sparing?

DR. SCRANTON: I could address that very quickly. Those are challenging. We are conducting a large registry with the Department of Defense and working with Dr. Buckenmaier. We actually are assessing patients at baseline. We're looking at pain catastrophizing. We're looking at other factors that may predict future outcomes.

In that registry of over 300 patients to date, we're also assessing PROMIS tools, both early and late, and we're following them upwards to over six months. And there what I hope is that we can begin to demonstrate -- if we can have a patient not experience severe pain and be exposed to opioids, and get them up and functioning, can that benefit longer term outcomes? I don't have the

answer to that yet, but we're beginning to study that.

Similarly at the University of Tennessee, we're also looking at that in hernia patients, patients who are coming in who've had chronic pain and going under revision surgery. If we can turn off that pain signal, provide education and multimodal and non-opioid, can we track different outcomes? That's just another partnership that we're working on, and that's what we're committed to do. And we're hoping we can show that you can make a difference from intense, non-opioid pain management early on.

DR. GULUR: One last question, Dr. Scranton. Toward that point, the active control studies to show -- I think we can all agree that pain control is important for better outcomes. Any thoughts comparing this to catheter, EXPAREL to catheter? I've seen studies that are comparing it to bupivacaine, but comparing it to catheters. And I understand that there was some question put on activity levels being impeded, but now you have

catheters, which have disposable pumps, and patients can go home with them comfortably.

Have there been any studies that compare the two and show improved outcomes?

DR. SCRANTON: I'll start with two examples, but I completely agree with you. When we began working with the DoD -- I have a bias toward the military -- we began to see a pattern. We were seeing reduction in the use of epidurals, for example, and a move towards TAP infiltration. And that's where we began to realize that perhaps the right comparator would be something that was also giving control for 24-48 hours.

We then observed the same pattern at Cleveland Clinic, where we've been using for over five years. We began to see a significant reduction in the use of epidurals -- go ahead and bring up that prior slide -- in which we were able to demonstrate a significant benefit. We designed this. It was an a priori, noninferiority study, where we looked at both reductions in pain, and that was an a priori difference in 1 in our pain

score, but also a reduction in opioids because it's not sufficient to say that we're as good as an epidural if they were taking more opioids.

So this was a paper that was published by Dr. Ayad, Dr. Sessler, and Turan, in which you can see here in red is the noninferiority margin where we're comparing the TAP administration with EXPAREL against an epidural, which that epidural also included a local anesthetic and opioids. We did demonstrate noninferiority with regard to pain and we were able to demonstrate noninferiority with regard to total opioid use consumption.

Now, this resulted in a publication also noting that patients were going home one day sooner on the EXPAREL arm. And we believe we've seen this consistently. Someone has to come and write the order to discontinue the epidural. You have to then make certain their pain is well controlled. We've seen this with PCA and spine patients, for example, so this is just another example.

We are now doing this as a multicenter randomized trial comparing EXPAREL against an

epidural, but we've added important additional outcomes. We're looking at the occurrence of hypotension with epidurals because even with perhaps not as good as an epidural, but we avoid hypotension and we avoid other complications from epidural, that may be a choice that some physicians may make. So that's an ongoing study.

So I completely agree with you. With approval with a nerve block, there may be settings where a catheter is the appropriate pain management for that person, but there will be other settings where we will evaluate where perhaps a single administration is more appropriate. And I think it's important to hear Dr. Gadsden talk about that in his popliteal nerve block, where that decision is being made today.

DR. GADSDEN: Thank you. We are beginning to see a transition to a different practice pattern with our total ankle patients, which I brought up before. Instead of doing a popliteal catheter and a saphenous catheter and sending them home for a couple days worth of local anesthetic in a bag,

we're now doing many more patients with a single injection of EXPAREL admixed with bupivacaine on both those sites. And what we're seeing when we follow these patients is they have an equivalent amount of pain control because, let's be honest, catheters when they work, work really, really well, but there's the caveat.

So we do see a number of catheters on the floor before patients go home getting displaced both in our knee patients, our shoulder patients, and our ankle patients. And this is resource intensive and requires us to go see the patient in their room or bring them down to the recovery room, and fix everything up, and send them back. And that takes time, it takes money, and it takes effort.

Imagine that happening at home, and we do get these, too. We follow these patients every day when they're at home, with a catheter or with EXPAREL, and we monitor and ask them all the right questions about how they're feeling and they're experience. And we see a number of patients that

it's quite obvious their pain score was low at this time point, but then jumped up, and yet the bag is still half full. So that's evidence of displacement. And in some cases, I've called those patients back in the hospital because I feel it's in their best interest to get those catheters replaced because I feel bad for them, and I want them to get the full experience.

We don't have to do that with EXPAREL because it's staying where you put it, and to me, that's one of the big advantages. I am fortunate enough to have been trained in how to do catheters, but not everybody is. And I think what is a remarkable thing about a formulation like this is it's going to put a big tool into a lot of people's hands that wouldn't ordinarily have that in their toolbox, and it ought to provide patients with a longer lasting relief postoperatively.

DR. McCANN: So it's almost 3:30, so I thought we'd take a 15-minute break and then finish up with a few more questions. I'll have everybody come back at 3:40. Thank you. And remember, don't

talk about anything.

(Whereupon, at 3:28 p.m., a recess was taken.)

DR. McCANN: Hello. We're back. The break is over. We're going to continue with some clarifying questions for Pacira, and we'd like to start off with Dr. Porter.

DR. PORTER: Thank you. My question's regarding total knee replacements. On the slide RW-7, I was just wondering what the age selection criteria was for -- sorry. Let me try that again; the demographics of the patients that were enrolled in the trial -- because it doesn't seem to me that it's -- I don't understand how somebody could receive the EXPAREL and then be able to go home the same day. If they have numbness, if there are side effects from it in their foot, in their leg, how they're able to ambulate quicker and go home. And what were the ages, and are there certain characteristics of people that are more likely to benefit from it than others?

DR. SCRANTON: In the PILLAR study, the

advantage of doing the local infiltration versus the regional nerve block, you're only numbing the fibers right there locally, so just the anterior part of the knee and posterior is being numbed. So they get full ability to move their foot and walk around, and that's how we were able to obtain that. When you do a femoral nerve block, you can get numbness that extended beyond the knee. And particularly when they used to do the sciatic, patients, it would be very difficult for them to get out of bed.

So that's why we think that for a very aggressive physical therapy program, a periarticular local infiltration with EXPAREL is probably better for the majority of patients. However, if you're having amputation and you're not getting enough ambulating, a femoral nerve block could give you that persistent effect that you need, and it would be appropriate in that setting.

DR. PORTER: Thank you.

DR. McCANN: Dr. Higgins, did you have another question?

(Dr. Higgins indicates no.)

DR. McCANN: All right. Dr. Zacharoff?

DR. ZACHAROFF: My question's been answered. Thank you.

DR. McCANN: Okay. I had my question about the liposomes.

DR. SCRANTON: Yes, ma'am, I do have that answer. Just to clarify, the cholesterol derived from sheep wool grease, we have a supplier from that. Then we take those lipids and we actually synthesize the multivesicular liposomes. So you can see from the depiction on the right, what we are able to achieve when using these is a biphospholipid layer very similar to how our cells compartmentalize themselves.

That's really the unique attributes of our multivesicular liposome. You have this lipid bilayer, and then we're able to change the cholesterol -- or we get the cholesterol. We change the triglyceride length, and that helps with the stabilization of the particle, and it gives us that extended-release preparation. When this is

broken down, bupivacaine is released, and we have now the DepoFoam particle there that is broken down just as any lipid was and taken up by the lymphatics.

DR. McCANN: Is there any safety information if it's injected intravascularly or intra-arterially even for other medications?

DR. SCRANTON: The DepoFoam has a depot site that we use for intrathecal administration, and that's been used for years. We haven't had any issues there. The DepoFoam, we haven't observed any evidence in human studies where there's been any issues of thrombolic events. Again, in our animal studies sites, where we did physically inject this intravascularly, we did not see any evidence of splenic infarcts or pulmonary infarcts from that injection.

DR. McCANN: Right. If I'm not mistaken, and I may be, I think when you presented the slide for intravascular injection, you presented 4 dogs; is that right?

DR. SCRANTON: Yes.

DR. McCANN: So you don't have really extensive experience injecting this into any creature.

DR. SCRANTON: In dogs for the intravenous administration we also have intra-arterial injection as well from the dogs. We didn't show that. We could depict that slide. We have the graph. But again, that was more looking at the PK, and we were not trying to sacrifice or euthanize those animals. It's just in our other smaller animal models, in rats or rabbits, where we haven't observed any intravascular disruption.

DR. McCANN: Do you have any idea the number of animals?

DR. SCRANTON: We did the 4 dog studies for the IV and similar for IA studies.

DR. McCANN: Thank you.

Are there any other questions for Pacira? Yes, Dr. Gulur?

DR. GULUR: Thank you, Dr. McCann.

Just one question related to intravascular injection. One of the concerns we have when we do

nerve blocks is inadvertent intravascular uptake or intravascular injection, bupivacaine being particularly concerning because of the cardiac effects that it can have the resuscitation issues with it.

We use intralipid to rescue those patients. How would we respond to intravascular injection of this formulation?

DR. SCRANTON: There was actually just a review done by ASRA where they put out their recommended guidelines, and they actually cite EXPAREL. They recommend you would treat it no differently -- if you're observing signs and symptoms suggestive of an intravascular injection and toxicity, to administer intralipid as you would because, again, the lipid component isn't going to impede the effect of the intralipid. And it is an lipid, so it's encapsulated. So as long as it's encapsulated, it doesn't have any effect; only the release component. So if you want to depot that with additional intralipid, then you would depot that with intralipid.

DR. GULUR: Is that a hypothesis or actually based on studies?

DR. SCRANTON: Our studies, when we demonstrate the effects, bupivacaine is encapsulated within the lipids, it doesn't cause depolarization of nerves. It's only the released drugs that can have that effect.

DR. GULUR: Thank you.

DR. McCANN: Are there any other questions for Pacira? Yes, Dr. Terman?

DR. TERMAN: I've got a couple. One, the investigator initiated study also was quite impressive. Were there any PK data that came along with those studies?

DR. SCRANTON: No. I don't have PK data from those two particular studies. That was part of their investigational plan.

DR. TERMAN: For those of us old enough to have used 0.75 percent bupivacaine, which certainly gave a much longer block duration but presumably much higher peak bupivacaine in the blood, it would have been nice to have seen some PK along with that

comparison between bupivacaine and EXPAREL, which is still pretty rate in the literature.

I guess the other question that I have has to do with -- although I'm very impressed with the three studies that I just mentioned, I'm much less impressed with the femoral studies. What I didn't hear in your presentation is much explanation for why -- if I'm thinking about using that for my femoral block, why I might not want to do that, because I didn't see much of an effect in the first study a couple years ago, and I didn't see any effect in the second study. So I'd be interested in more about what was going on there in your opinion.

DR. SCRANTON: We can bring up the 323 study, our original. One of the challenges with the femoral nerve block is the fact that it's not an ideal place to study the effectiveness of EXPAREL because it's not covering the complete pain. They still have posterior pain.

If you could bring up the 323 study. That was our challenge, and that was actually the first

study that we had observed the fact that we also didn't see a difference in time to first opioid rescue. As you can see here, this is the effect that we observed, but we did observe a significant reduction in pain through the entire duration of 72 hours, but we're still not covering posterior pain.

So from a patient's perspective, if they're waking up and they had no anterior knee pain but they have pain in the posterior knee, they had pain. So that also results in opioid rescue, and it's also why we don't believe we solved the most as-robust reduction in opioid reduction because people tend to rescue those patients.

If we could show the non-imputed data from 323 as well. Bring up the 323 non-imputed. Even in 323, however, in the non-imputed, when you're looking here, you're seeing, by and large, patients are having mild pain and you're seeing the marked reduction of opioids. So we're actually seeing reduction in opioids as well as that reduction in pain. And that's the important part; that I still

believe in this study we demonstrated the primary endpoint of the duration of pain through 72 hours in the face of also reducing opioids.

Again remembering 331, when we did an infiltration, where we covered both anterior and posterior, we showed marked reduction in pain and a 78 percent reduction in opioids. So I think those are the key challenges of doing a femoral nerve block.

DR. TERMAN: If you go back to that slide again, you're going to tell me that those later time points are significantly different from one another?

DR. SCRANTON: I can show you the different time points. With 323, we looked at the time points; again, multiple testing, but we can bring up the summary of pain scores at each time point.

Here, I can demonstrate at each time point after 323 -- 12 -- you may have overlapping confidence limits, but it still made statistically significant. This is just demonstrating that there were differences in pain at each time point. And

Dr. Conner can speak to the statistical significance of these findings in lieu of all of our studies that we've done if that would help.

DR. TERMAN: And this is back to the imputed -- the data analysis where you keep the -- is it this slide, that table? Is that this slide or is it a previous slide where you kept the pain score the same after each dose of opiate?

DR. CONNER: Right. I can answer that. This is Jason Conner. Right. This uses the primary analysis method, which does impute forward than when patients were on opioids. And I think one key is later on, there is a liberal use of opioids in general, and clinicians and nurses tend to titrate to the pain.

Can we have PE-12 again? I think one key is when those curves were coming together with the raw data, we're still seeing a difference in opioids at that later time point. So much of the coming together is because patients are on opioids then or, rather, were titrating the pain, but there's a difference in the amount of opioids necessary to

reach those pain levels.

DR. TERMAN: Do you have a similar slide or two on the time course in the 326 study where you didn't see a significant effect?

DR. CONNER: Can you tee up 17 for me? Sorry, this is 326. Here we go. This shows the without imputation. I don't know if we have opioids; maybe we can get that for you, but without imputation here, you can see where that difference is, and pain is higher in placebo patients.

One of the interesting differences in this study was in 323 -- sorry -- in 327, we saw the doctors and clinicians tended to wait until a patient was around 6, a median of 6, to the first time they used rescue opioids, and in 326, rescue opioids were used at a median of 4. So it seems like the clinicians were intercepting the pain before pain got too high. And in fact, in the 326 study, the first quartile was just 1.8, so 25 percent of patients were getting an opioid before their pain even got to 2. So that's one reason why this was particularly low and then

difficult to see a difference.

DR. TERMAN: Thank you.

DR. McCANN: Before we adjourn for the day, are there any last comments from the FDA?

DR. HERTZ: Thanks, but no. Thank you all. We look forward to seeing you in the morning.

Adjournment

DR. McCANN: The meeting for today is now adjourned. Panel members, please remember there should be no discussion of the meeting topic amongst yourselves or with any member of the audience. Please take all your personal belongings with you as the room is cleaned at the end of the meeting today. All materials left on the table will be disposed of. We will reconvene tomorrow morning at 8:00 a.m. Thank you for all your help.

(Whereupon, at 3:55 p.m., the meeting was adjourned.)