FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE (AADPAC) MEETING

Thursday, February 15, 2018

Day 2

8:00 a.m. to 2:56 p.m.

FDA White Oak Campus

Building 31 Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. McCANN: Hello. Good morning. I would like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Tara Rabin. If you are here, 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 will start by going around the table and introducing ourselves. We will start with the FDA on my left and go around the table.

DR. HERTZ: Good morning. I'm Sharon Hertz, director for the Division of Anesthesia, Analgesia, and Addiction Products.

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

DR. BAZINI: Good morning. This is Alla Bazini, and I'm a clinical reviewer in the same division.

MR. PETULLO: David Petullo, statistical team leader, Office of Biostatistics.

DR. XU: Yun Xu, team leader, Office of Clinical Pharmacology.

DR. SHOBEN: Good morning. I'm Abby Shoben, and I'm an associate professor of biostatistics at Ohio State.

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

DR. LITMAN: Good morning. Ron Litman. I'm an anesthesiologist at the Children's Hospital Philadelphia, University of Pennsylvania, and I'm the medical director of the Institute for Safe Medication Practices.

DR. CHOI: Moon Hee Choi, designated federal

officer.

DR. McCANN: Mary Ellen McCann. I'm a pediatric anesthesiologist at Boston Children's Hospital and an associate professor at Harvard Medical School.

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

DR. HIGGINS: Jennifer Higgins, AADPAC consumer representative.

DR. PORTER: Laura Porter, patient representative.

DR. TERMAN: Greg Terman, professor of anesthesiology 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: Good morning. Kevin Zacharoff, anesthesiology and pain medicine, faculty and clinical instructor at SUNY Stony Brook School of Medicine.

DR. GULUR: Good morning. I'm Padma Gulur. I'm professor of anesthesiology at Duke University and medical director of the pain services.

DR. HUMMEL: Good morning. Michele Hummel. I'm a pharmacologist. I'm the outside industry rep.

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

Now, we now pass 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 discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as

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

Today's agenda involves discussion of supplemental new drug application sNDA 022496/S-009, for EXPAREL, bupivacaine liposome injectable suspension, submitted by Pacira Pharmaceuticals to produce local analgesia and as a 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 would 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 morning. Dr. McCann, members of the AADPAC, invited guests, welcome. We will continue our discussion of EXPAREL, bupivacaine liposomal injection suspension today. As I noted yesterday, 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 I mentioned yesterday, there are some differences in opinion on how to interpret the results of these studies. This morning you're going to hear the presentations from FDA, then we will have some additional discussion.

When a new formulation of a previously approved drug substance is studied, in general, we think the clinical trials should reflect the changes that distinguish the new product from the existing approved drug substance in other formulations. Throughout development, we've

requested the applicant include an active comparator arm in their clinical studies, and unfortunately we don't always have the ability to require it. So while we may agree that a protocol is acceptable, it doesn't necessarily mean it's ideal.

Today you'll hear again about the four nerve-block studies, including the two new studies that were done following the initial complete response, and we're also going to go over some of the prior studies that were done for infiltration, which we think are going to help describe some of the interpretation for one of the new nerve-block studies. Key issues that will be highlighted will be what are the efficacy data that may or may not support a nerve-block indication and are there data that support the change. It's a subtle change but potentially an important change in the original indication.

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. So as you consider the efficacy data, we're also going to ask for your thoughts about what constitutes a clinically meaningful opioid-sparing effect across the data that we will be presenting. We think it's important because we think it's important for prescribers to have a full understanding of the effects of the new product and what the product is capable of doing.

Once again, I'll say this now, and I'm going to say it multiple times. We really appreciate the time you take from very busy schedules, and thank you for participating.

DR. McCANN: We will now proceed with the FDA presentations.

FDA Presentation - Alla Bazini

DR. BAZINI: Good morning, everybody. My name is Alla Bazini. I am a clinical reviewer with the Division of Anesthesia, Analgesia, and Addiction Products. I'm also a practicing pediatric anesthesiologist.

This morning I'm going to start off the background and overview of this presentation. I will present the background of the sNDA application. I will then introduce the four pivotal studies. Katherine Meaker will present the statistical overview of the study results. I will return to discuss possible etiologies for the femoral nerve-block study failure, the supporting studies, and the opioid-sparing data. Dr. Naraharisetti will then present pharmacokinetic data, which is pertinent to the safety profile of EXPAREL. I will then return to discuss the safety data and the pivotal studies, local anesthetic systemic toxicity, and make our final conclusions.

Prior to discussing specific efficacy results, I would like to highlight these general comments as they are key points that you will see recur during both the safety and the efficacy discussions. Clinical studies for infiltration demonstrate a PK profile of EXPAREL that differs based on anatomical site of injection, and total systemic absorption of bupivacaine from EXPAREL is

dependent upon total dose, route, and vascularity at the site of adminsitration. The efficacy of the drug results from local exposure, whereas the safety is based both on local effects and systemic bupivacaine exposure.

The initial EXPAREL NDA was approved in 2011. There were several studies submitted with outcomes for infiltration. There were five phase 2 active control studies with bupivacaine; there were three phase 3 active control studies with bupivacaine; there were two phase 3 placebo-controlled studies with no active comparator; and there was one phase 2 active control study with outcomes for ankle block.

In these slides, I will summarize the active control studies. In this first table, there are four phase 2 infiltration studies that we're looking at: hernia repair, total knee arthroplasty or TKA, or hemorrhoidectomy. They compared doses of up to 532 milligrams of EXPAREL to quarter percent bupivacaine, and all by infiltration. None of these studies demonstrated clinical or

statistical difference in the study groups.

This table lists additional two phase 2 studies where EXPAREL was compared to bupivacaine for breast augmentation and bunionectomy. I will discuss the first study listed in more detail in the next slide. The second study, study 203, failed to show a statistical difference between EXPAREL and bupivacaine when given via ankle block.

I'm highlighting study 210 because there was some disagreement regarding the study results. This was a phase 2 study comparing EXPAREL 133 and 266 milligrams to three-quarters percent bupivacaine for breast augmentation. There were two control groups that were matched for volume. Because this was a phase 2 study, there were no prespecified endpoints.

The applicant claims that the study demonstrated EXPAREL was superior to bupivacaine. A closer look at the data however revealed that only several random statistically significant p-values were present, and they were present at different time points that were not consistent

across groups or over time. Therefore, the totality of the data for the study do not demonstrate a consistent statistical or clinical difference between the study groups.

This table lists the phase 3 infiltration studies that had bupivacaine active control in either TKA, hemorrhoidectomy, or breast augmentation. All had efficacy endpoints of the area under the curve, AUC, of the numerical rating scale or NRS pain score. None of these studies demonstrated a clinical or statistical difference between EXPAREL and bupivacaine.

To summarize, the applicant was not able to demonstrate superiority of EXPAREL to bupivacaine, however, the use of active control historically is not a requirement for drug approval. Therefore, the original NDA was approved in 2011 based on superiority of EXPAREL to placebo in two phase 3 studies, one in hemorrhoidectomy and one in bunionectomy.

In 2014, the applicant submitted an efficacy supplement for a new indication post-surgical

analgesia via nerve block. The supplement included two phase 3 studies. Study 322 evaluated the use of an intercostal nerve block in subjects undergoing posterolateral thoracotomy. This study failed to demonstrate the efficacy of EXPAREL against placebo.

Study 323 evaluated the use of femoral block in subjects undergoing total knee arthroplasty. This study was able to demonstrate the efficacy of EXPAREL against placebo, however, failed to adequately address the safety of EXPAREL given via femoral nerve block. Specifically, the median time of maximum concentration, or Tmax, was greater than the 72-hour period of assessment planned in the study protocol. The assessments of systemic toxicity were intended to continue through Tmax, but they ceased at 72 hours for most patients.

There was inadequate capture of plasma bupivacaine concentrations at the time of cardiac or neurologic symptoms, there was inadequate reporting of cardiac safety data, and there were inadequate data to characterize the onset and

duration of femoral block. I will discuss these issues in more detail and additional safety data later this morning. However, due to these reasons, the sND application received a complete response in February of 2015.

In the next several slides, I will present more details regarding studies 322 and 323. Study 322 evaluated the intercostal nerve block. Subjects were randomized equally to EXPAREL 266 or placebo, and there was no bupivacaine comparator group. The study was mostly conducted in several eastern European countries.

The primary efficacy endpoint in this study was the area under the curve of the pain intensity score NRS through 72 hours. As you can see, there was no statistical difference between two study groups. Katherine Meaker will discuss the meaning of the area under the curve a little later this morning.

The applicant provided several explanations for study failure in their sNDA submission, and they are listed on the slide. Baseline

pre-surgical pain scores were lower in Bulgaria and the Czech Republic. According to the applicant, when Bulgaria and Czech Republic were excluded in a post hoc analysis, the difference from placebo was statistically significant. However, because the study subjects were undergoing open thoracotomies, the protocol appropriately excluded subjects that had concurrent painful physical conditions or concurrent surgery that may require analgesic treatments; for example, cancer pain, neuropathic pain, or concurrent abdominal surgery. Therefore, baseline pre-surgical pain should have little to no correlation to postoperative pain this particular clinical setting.

As opposed to other studies, these blocks were not performed by anesthesiologists using ultrasound guidance but rather the surgeons who were performing these blocks under direct visualization immediately prior to surgical closure and to the index nerve as well as the nerve immediately above and immediately below.

In the Integrated Summary of Efficacy, the

applicant stated that they believe that the variable technique of injection by the surgeons and imprecise placement that resulted from direct visualization as opposed to ultrasound contributed to failure of the study to show efficacy. This rationale seems unlikely given that, intuitively, direct visualization would only enhance rather than diminish the accuracy of the block.

Another reason provided by the applicant was the supine positioning of the patients rather than prone. Although intercostal nerve blocks are often performed in prone position, there is literature that indicates that block can be performed successfully in prone, lateral, sitting, or supine positions. And finally, the most clinically relevant explanation is the extremely short time to max concentration variability in the PK data observed, which suggests that the drug was absorbed and cleared very quickly. Given that the drug was administered into a highly vascular field, this explanation makes the most sense.

I will move on to discuss study 323 in the

femoral nerve block for total knee arthroplasty. The study had two parts, part 1 being a phase 2 dose-finding study and part 2 was the phase 3 efficacy study. Part 2 EXPAREL 266 milligrams was compared to placebo. There was no bupivacaine active comparator group. The primary efficacy endpoint in this study was the same as study 322 or the AUC of NRS-R through 72 hours.

As you can see, this study met statistical significance, however, I would like to point out the difference in the values of the AUC is less than 100. Katherine Meaker will present the pain intensity curves later this morning that will further demonstrate the narrow albeit statistically significant difference, which really questions the clinical significance of these results.

There were two secondary endpoints evaluated, time to first opioid rescue and total post-surgical opioid consumption and intravenous morphine equivalents. Although there was a statistically significant difference in time to first opioid in part 1 of the study, part 2 failed

to demonstrate a difference. The applicant proposes that this endpoint failed because subject had intact sensation in the sciatic distribution and therefore experiencing pain in the posterior aspect of the knee.

This is one possible explanation, although it doesn't explain why the difference was observed in part 1 of the study. Another possible explanation is that the onset of the femoral nerve block was simply delayed such that the subjects awoke with intact sensation in the femoral distribution.

For total opioid consumption, there was only statistically significant difference in part 2 of the study. The placebo group used 122 IV morphine equivalents, whereas the EXPAREL group used 93, which is still a significant amount of opioids. Therefore, albeit statistically significant, the clinical significance of this difference is also questionable. I would also like to point out that no subjects in the study groups remained opioid free, and Kate Meaker will present additional

details regarding these results shortly.

To summarize, the applicant received a complete response and 2014 efficacy supplement because they failed to adequately characterize efficacy of EXPAREL for the proposed indication since they only had one study in the femoral nerve block that met its primary efficacy endpoint. In addition, the applicant failed to characterize the safety of EXPAREL in the femoral nerve block for broader nerve-block indication.

In the complete response letter, the applicant was advised that in order to pursue the proposed indication, they would need to provide evidence of efficacy and safety from an adequate and well controlled study in at least one additional clinical setting. In addition, the applicant would need to conduct a clinical trial in femoral nerve block in which clinical safety outcomes are followed until the upper limit of Tmax or resolution of the block, as well as include assessments of sensory and motor function that demonstrate the onset and resolution of the sensory

and motor deficits from the nerve block.

To address the deficiencies in the complete response, the applicant resubmitted a supplement NDA in 2017 with two new phase 3 studies. Study 326 enrolled patients undergoing total knee arthroplasty and administered a femoral nerve block. Study 327 enrolled patients undergoing total shoulder arthroplasty or a rotator cuff repair and administered a brachial plexus block. In addition, the applicant submitted two supportive studies, 1601 and 1602, in the median and ulnar nerve blocks, posterior tibial, and deep peroneal nerve blocks, respectively.

These were investigator initiated studies that were sponsored by the applicant in which EXPAREL was actually admixed with bupivacaine. I will discuss the pertinent aspects of these supportive studies following the discussion of the pivotal studies.

Before I go into the details of the two new studies, I would like to point out some important differences between the indications. The approve

indication is for infiltration into the surgical site for post-surgical analgesia. The proposed indication in the previous cycle was for local or regional post-surgical analgesia when administered into surgical site or as a nerve block. However, the newly revised proposed indication does not have a post-surgical component, which could be interpreted that EXPAREL may be used in any setting that local or regional analgesia is indicated.

None of the pivotal studies conducted by the applicant evaluated the use of EXPAREL in a non-surgical setting, and the applicant has not provided a rationale to justify extrapolation of either efficacy or safety data to a non-surgical or office-based setting.

Let's talk about the new studies. Study 326 was the femoral nerve study and TKA. Subjects were randomized equally to EXPAREL 133, 266, or to placebo. Although there wasn't a true active comparator, all subjects did receive additional 40 milligrams of bupivacaine that was given via the posterior capsule by the surgeons. You can see the

adjusted total bupivacaine doses here.

Since study 326 was the repeated femoral nerve-block study, I would like to point out the pertinent differences between the two studies. In study 323, non-opioid analgesics were not permitted and no additional local anesthetic was administered. In study 326, all subjects received cyclobenzaprine and acetaminophen or paracetamol. In addition, all subjects received additional bupivacaine via posterior capsule.

The results of both femoral nerve-block studies are presented in this table. I would like to remind everyone that the applicant proposed a new conversion schema for IV morphine equivalents for the two new studies, which you just heard about yesterday. However, we have not had an opportunity to review this new proposal, so the numbers of IV morphine equivalents throughout this presentation is based on the original conversion schema submitted by the applicant to this sNDA.

As you can see, unlike study 323, there were no statistically significant differences between

the study groups for the primary or secondary endpoints. The applicant provided several hypotheses as to why study 326 did not meet these endpoints, and I will discuss these a little bit later. However, given that the most clinically important difference between the studies was the addition of bupivacaine hydrochloride via the posterior capsule in study 326, it seems reasonable to attribute the lack of difference between the study groups to this bupivacaine.

In other words, EXPAREL administered via femoral nerve block appears to have no advantage over bupivacaine administered via posterior capsule for postoperative management in the first 72 hours after total knew arthroplasty.

The final pivotal study I will discuss is study 327 in the brachial plexus nerve block. The subjects were originally randomized to EXPAREL 133, 266, or to placebo. Again, there were no bupivacaine comparator groups. However, the 266-milligram cohort was continued after 15 subjects because interim PK data demonstrated

prolonged Tmax of 60 hours in this arm. Additionally, around the same time, the study was published demonstrating the efficacy of a lower dose of EXPAREL for interscalene nerve block.

I would like to point out that the study endpoints evaluated pain and opioid use for only 48 hours, whereas the other three pivotal studies evaluated these endpoints for 72 hours. The study results demonstrated a statistically significant difference in all study endpoints at 48 hours. Katherine Meaker will present data for these endpoints for 72 hours in which the secondary endpoint of opioid-free subjects becomes no longer statistically significant.

In addition, although the difference in time to first opioid was statistically significant, we are talking about 3 and a half hours here, not days. It's unclear whether there is any benefit of a 3 and a half hour difference in the context of the other clinical data.

Now that I have covered the background of the pivotal studies, I will pause, and I'll let

Katherine Meaker present more details regarding the statistical review of efficacy data.

FDA Presentation - Katherine Meaker

MS. MEAKER: Thank you, Dr. Bazini.

Good morning. My name is Kate Meaker. I'm a statistical reviewer here at the Center for Drugs. I'm going to be talking about the pertinent results of the statistical analyses of the four phase 3 EXPAREL nerve-block studies. Dr. Bazini has already discussed the study designs and surgical settings of these studies.

The area under the curve, referred to as AUC, represents the cumulative pain over time. It is a function of both the observed pain intensity measured on a 0 to 10 numeric rating scale or a 0 to 10 centimeter visual analog scale and the length of time included in the target time frame. The average pain can be calculated by dividing the AUC by the number of hours, but cumulative pain over time, as represented by the AUC measure, is more relevant for our consideration of efficacy of reduction of post-op pain.

One study, the brachial plexus nerve study 327 was planned with 0 to 48 hours as the primary efficacy time frame. The other three studies were planned with 0 to 72 hours as the primary time frame. For ease of discussion across the studies, I will report the results for the 72-hour postoperative period for all four studies. In almost all results, the conclusions at 48 hours and 72 hours were consistent, which I will note during my presentation.

Pain intensity was reported on a 0 to 10 scale with zero being no pain and 10 being worse pain. A statistically significant difference between EXPAREL and placebo was demonstrated in the brachial plexus nerve-block study 327 with a difference of 145 units, which equates to a mean difference of two units averaged across a 72-hour time frame.

In study 323, the femoral nerve-block study without bupivacaine posterior capsule injection, a statistically significant difference of 97 units in the AUC or 1.3 units averaged across the 72 hours

was demonstrated. Dr. Bazini will discuss the clinical relevance of these results. The other two studies did not show differences between EXPAREL groups and placebo for reduction of post-op pain.

I will now briefly discuss the two femoral nerve-block studies, one of which showed a statistical significant treatment effect and one did not. The applicant conducted several post hoc subgroup analyses in an attempt to explain why the more recent femoral nerve-block study 326 failed to show a significant treatment effect. A key difference in the designs between the two femoral nerve-block studies was the inclusion of bupivacaine posterior capsule injection during the surgical procedure in study 326.

In the sNDA submission, the applicant discussed the multiple post hoc subset analyses suggesting plausible explanations for why no difference was found between either EXPAREL arm and placebo. The unplanned analyses included pre- and post-randomization characteristics shown here. Dr. Bazini will discuss the rationale given for

these multiple post hoc analyses. These are not statistically valid analyses to support conclusions and should only be considered exploratory.

I return now to the pain assessments for each of the four nerve-block studies. I will show mean pain at several time points across the 72-hour time frame. Time is displayed on the horizontal axis. Mean pain with 95 percent confidence interval bars is shown on the vertical axis. As shown here for the intercostal nerve-block study 322, the lines do not separate. This confirms the conclusion from the analyses of the AUC pain that there are no statistical differences in reduction of pain between these treatment groups.

This figure displays mean pain across time for the femoral nerve-block study without the bupivacaine posterior capsule injection. The lines remain separate across the 72-hour time frame confirming that there is a statistically significant difference in reduction of pain between the EXPAREL 266-milligram group and placebo in this study.

This figure displays mean pain across time for the femoral nerve-block study 326 with bupivacaine posterior capsule injection as part of the surgical procedure. The lines do not separate across a 72-hour time frame confirming that there is no statistically significant difference in reduction of pain between the EXPAREL 133-milligram or 266-milligram group and placebo in this study.

To compare the results from the two femoral nerve-block studies, the results from the previous two slides are combined here. The top two lines are from study 323 and show a separation in the mean pain scores. Patients in this study did not receive the posterior injection of bupivacaine. The bottom three lines are from study 326, and as you clearly see do not show separation, indicating no difference between the two EXPAREL arms. Note, all patients in this study received the injection of bupivacaine in the posterior capsule.

As you can see, regardless of treatment, subjects in study 326 on average appeared to have less pain than subjects enrolled in study 323.

This could be due to the posterior injection of immediate-release bupivacaine. Dr. Bazini will discuss this in more detail.

Returning to the brachial plexus nerve study 327, the lines clearly separate confirming the analyses of the AUC pain endpoint. Note that the primary endpoint was defined at 0 to 48 hours and showed a statistical difference between the groups in AUC pain. This separation observed through 48 hours extended through 72 hours.

In addition to looking at post-surgical pain, we are also interested in the use of opioid rescue medication during the 72-hour postoperative time frame. We did not take into account whether or not these endpoints were specified as primary, secondary, or key secondary. These endpoints are clinically important, and the results will be presented without consideration for multiplicity. This means any p-values presented are compared to alpha equals 0.05 and are not adjusted for multiple comparisons or hierarchical testing.

The outcomes we considered to assess opioid

rescue are the total amount of opioid rescue converted to morphine-equivalent dose in milligrams, the proportion of subjects who did not use opioid rescue through 72 hours, and the time until use of first opioid rescue.

This table shows the total post-surgical opioid consumption in IV morphine equivalents through 72 hours. The conversion of all forms of opioid rescue to morphine-equivalent doses in milligrams was consistent across the four protocols as presented here. This does not incorporate the new schema proposed by Pacira last Friday, which is included in their errata.

As in analyses of the pain outcome, the same two studies showed a statistically significant difference in the amount of total opioid consumption over the 72-hour time frame. In the brachial plexus nerve-block study, the EXPAREL 133-milligram group used an average of 97 milligrams less opioid rescue than placebo group. In the femoral nerve-block study without bupivacaine posterior capsule injection, the

EXPAREL 266-milligram group used an average of 27 milligrams less opioid rescue than the placebo group. Dr. Bazini will discuss the clinical relevance of these reductions in opioid use.

This figure shows the cumulative post-surgical opioid consumption by treatment group and by study broken out by three time frames. In each panel, the solid dot represents the mean cumulative dose as morphine equivalents. The bars show the upper and lower bound of the 95 percent confidence interval. Each column shows the single study at three different time points, 0 to 24 hours at the bottom, 0 to 48 in the center, and 0 to 72 hours at the top. Only the brachial plexus nerve-block study, the left-hand column, study 327, shows clear separation between the treatment groups and is consistent across the three post-surgical time frames.

While the femoral nerve-block study without bupivacaine posterior injection, study 323, which is shown in the third column here, showed statistically significance at 72 hours, the

separation is not as large or clearly differentiated as in study 327. I will show each of these two studies in larger detail next.

This shows the total opioid consumption for just study 323, the femoral nerve-block study without bupivacaine injection. The axes are switched from the previous figure. Here the total amount of opioid rescue is on the vertical axis with the time frames on the horizontal axis. While the analyses of AUC pain through 72 hours concluded statistical significance, the separation between the two groups is not as distinct as in study 327, which I will show next.

This presents the cumulative opioid consumption results for the brachial plexus nerve study 327. There was clear separation between the treatment groups, which is consistent across the three post-surgical time frames. Again, Dr. Bazini will discuss the clinical relevance of these differences.

This table gives the number and percent, where not zero, of patients who did not use opioid

rescue through 72 hours post-surgery. None of the studies showed a statistically significant difference for the EXPAREL dose groups versus placebo for this endpoint at 72 hours. In all four studies, almost all the patients used opioid rescue by 72 hours post-op.

The final outcome of interest regarding post-surgical opioid use is the time to first rescue. As noted on the previous slide, almost all patients in these four studies used opioid rescue, so there's little censored data. Neither of the femoral nerve-block studies demonstrated a statistically significant difference in the time to first rescue between EXPAREL and placebo treatments. Two studies, the brachial plexus and the intercostal nerve-block studies, did show statistical significance for time to first rescue. For these two studies, I will display the time curves to demonstrate the actual differences observed.

In the intercostal nerve-block study 322, the difference in median time to first rescue was

less than half an hour, shown by the separation of the lines at the far left of this graph. This figure shows the separation of the time to first rescue curves in the brachial plexus nerve-block study. The difference in median time to first rescue is about 3 and a half hours.

This slide presents the conclusions from the statistical analyses of the pain and opioid use endpoints through 72 hours post-op. As previously mentioned in studies 327 and 323, treatment with EXPAREL when compared to placebo demonstrated a statistically significant reduction in postoperative pain and total amount of post-surgical opioid use through 72 hours. In study 327, treatment with EXPAREL also demonstrated a significant difference in the time to first use of opioids compared to placebo. In all four studies, most if not all patients used opioids by 72 hours post-op.

Now I will turn the presentation back to Dr. Bazini to discuss the clinical relevance of these findings.

FDA Presentation - Alla Bazini

DR. BAZINI: Although you have already seen the results for the first femoral nerve-block study, study 323, I would like to reiterate that statistically this study did meet its primary efficacy endpoint as well as the secondary efficacy endpoint of total opioid use in 72 hours. However, as you just saw, the actual pain score differences between the two study groups were only around 1 to 2 points across the entire 72 hours. This amount of difference is unlikely to have meaningful clinical impact on clinical outcomes. In addition, no subject remained opioid free and total opioid consumption was still considerable in the EXPAREL arms.

As I previously mentioned, the applicant provided numerous possible explanations as to why the second femoral nerve-block study failed to show efficacy, which I will present on the next several slides. The first rationale provided was that the new protocol required an extended hospital stay. Per applicant, the required length of stay caused

difficulty in recruitment of investigators that were experienced with EXPAREL. However, recent literature indicates that length of stay after primary joint arthroplasty is approximately 3.7 days and varies significantly due to numerous surgical or patient related factors.

In addition, the previous study 323 was the first femoral nerve-block study with EXPAREL, so the investigators were also not experienced with giving EXPAREL via femoral nerve block, however, that study was able to meet its primary efficacy endpoint. In addition, it is unlikely that any appropriately trained anesthesiologist would not have experience placing femoral nerve blocks, particularly because the technique of nerve-block administration did not differ significantly.

Another possible reason for study failure provided by the applicant is the difference in the U.S. and rest of the world or ROW populations. Specifically, the U.S. had higher mean baseline pain scores, prior opioid consumption, weight, and ASA class. However, when we analyzed the U.S. and

rest of the world population separately, we were still unable to demonstrate a treatment effect within each study region.

In addition, similar baseline patient characteristics were described in study 327 where 25 percent of the study population were enrolled in the same European study centers or study 326. And again, as we saw, that study did meet its statistical significance.

Another possible reason for study failure listed by the applicant is improperly performed posterior capsule injections at the Belgian site. In the Integrated Summary of Efficacy, the applicant stated that Belgian subjects had lower plasma bupivacaine levels in the PACU suggesting differences between sites in effectiveness of the posterior capsule injections. The applicant further stated that when they performed a post hoc analysis where subjects with PACU levels of less than 70 were eliminated, efficacy was met only for the 266-milligram group.

Kate Meaker had already discussed the

potential issues with unplanned post hoc analyses, and again, I'd like to reiterate that we know that plasma bupivacaine levels do not correlate with local drug efficacy. However, we did repeat the same subgroup analysis with both treatment arms, and no treatment effect was observed.

Another possible reason for study failure listed by the applicant is that some nurses at the Belgian site instructed subjects to take rescue medications and administer double doses of oxycodone. Oxycodone is not used for post-op pain at the Belgian site typically, so it's possible that nurses may have administered incorrect doses. However, when you look at just oxycodone dosing by U.S. and rest of the world, the mean doses were not significantly different and the median doses were exactly the same.

The final reason for study failure presented by the applicant is the difference in the pain scales utilized at the rest of the world sites. Specifically, the NRS scale was used instead of the VAS scale in the majority of subjects during

numerous pain assessments. The applicant was not able to identify which subjects had which scale used on the case report forms.

Since there is no standardize way to scale the two different pain scores, we cannot rely on the data from the Belgian site for efficacy analysis. So once again, when we removed the Belgian site from the efficacy analysis, the results were the same, meaning no treatment effect was observed.

In summary, the rationale provided by the applicant does not appear to fully explain the differences in efficacy observed in the two femoral nerve-block studies. The two important differences between the studies is the addition of bupivacaine via posterior capsule and the multimodal pain approach in the second femoral nerve-block study, study 326.

As I presented earlier this morning, there's also a historical trend in the applicant's development program where all nine studies conducted to date that utilized bupivacaine active

control failed to demonstrate clinical or statistical difference between EXPAREL and bupivacaine. Therefore, based on the data available, EXPAREL administered via femoral nerve block appears to have no advantage over bupivacaine administered via posterior capsule in the first 72 hours after total knee arthroplasty. In addition, no opioid-sparing effect was demonstrated.

Unlike study 326, study 327 met statistical significance on all primary and secondary endpoints in the first 48 hours. There were no major differences in efficacy between study regions or in the patient subpopulations. In the first 48 hours, 9 subjects in the EXPAREL remained opioid free and one subject in the placebo arm.

Although the result was statistically significant, the difference in 8 subjects is not clinically meaningful since the vast majority of subjects still required opioids. Furthermore, when the time period was widened to 72 hours like the other pivotal studies, only 4 subjects in the

EXPAREL arm remained opioid free compared to one in the placebo group. This is not statistically significant.

I will now briefly discuss the supportive studies submitted by the applicant. Study 1601 compared the admixture of EXPAREL plus bupivacaine, first as bupivacaine alone in subjects getting median and ulnar nerve blocks for Dupuytren's contracture release. It should be noted that this study, as well as study 1602, which I will discuss next, were conducted in Belgium, and the PI and sub-investigators of the study were the same investigators as the Belgian sites in study 326 and 327.

Although the total volume of the injected is 15 mL in each study group, you will notice that the EXPAREL-bupivacaine group received more than double the total milligrams of bupivacaine with the regular bupivacaine group getting 75 milligrams total and the bupivacaine-EXPAREL group getting 155 milligrams total. There were several efficacy endpoints evaluated, and multiple assessments were

performed through day 7.

The study results demonstrated that additional local anesthesia was required in most of the subjects in the bupivacaine-alone group as compared to only 3 subjects in the EXPAREL-bupivacaine group. In addition, worse pain over the first 72 hours was lower in subjects in the EXPAREL-bupivacaine group than in the bupivacaine-alone group. Finally, numbness persisted through day 3 and 4 in the EXPAREL-bupivacaine group, whereas it was mostly resolved by 48 hours in the bupivacaine-alone group.

These results seem significant, although I would like to point out that this study only contained 16 subjects for study group. In addition, as I already mentioned, there was a large discrepancy in total bupivacaine dose administered between the study groups, and therefore it's not surprising that the subjects who received more than double the dose of bupivacaine had a better outcome.

Study 1602 also compared an admixture of

EXPAREL plus bupivacaine versus bupivacaine alone or versus general anesthesia in subjects getting posterior tibial or deep peroneal nerve blocks for hallux valgus osteotomy. Once again, you can see the large difference in the milligrams of bupivacaine administered between the study groups. The efficacy endpoints were similar to study 1601, however, they also looked at the opioid consumption.

The results of this study demonstrate that mean opioid consumption in the postoperative period varied among the three study groups, where the subjects in the general anesthesia group had most use. This is not surprising. Patients reported worse pain, however, over the 72 hours was not significantly different between the EXPAREL-bupivacaine and the bupivacaine-alone groups, whereas persistence of numbness was more prominent in the EXPAREL groups versus the bupivacaine group alone.

Similar to study 1601, study 1602 had a small sample size. And again, the large

discrepancy in the total milligrams of bupivacaine administered between the study groups was the likely reason for any differences in the efficacy observed.

Katherine Meaker already presented the opioid-sparing data from the pivotal studies. I would like to discuss the clinical implications of this data. We are all aware that there is an opioid crisis going on in our nation. We know that uncontrolled acute pain may lead to development of chronic pain. It has also been postulated that post-surgical opioid use may be linked to subsequent persistent use.

A retrospective study by Alam and colleagues was performed in Canada looking at postoperative pain medication use data, both opioid and non-opioid, in subjects who were over 66 years of age getting ambulatory surgery. Their analysis revealed that previously opioid-naive patients prescribed opioids in the first 7 postoperative days were more likely to be using opioids at one year. However, the same conclusion was also made

for those who were prescribed NSAIDs. One possible interpretation of this data is that the use of analgesics in the first 7 postoperative days is more likely due to pain than the selection of the analgesic.

In another study, Dr. Brummett and colleagues examined nationwide insurance claims data from 2013 and 2014 for opioid use in U.S. adults prior to or after minor and major surgical procedures. They were able to demonstrate persistence of opioid use in previously opioid-naive patients at approximately 6 percent and 90 days versus 0.4 percent in the non-surgical comparator group. However, what they also found was that since persistent opioid use was not significantly different between minor and major surgical procedure groups, it may be reasonable to conclude that persistent opioid use does not appear to be associated solely with post-surgical pain but rather addressable behavioral and pain disorders.

Specifically, the risk factors that were independently associated with the new persistent

opioid use were preoperative tobacco use, alcohol and substance abuse disorders, mood disorders, anxiety, and preoperative pain disorders such as back pain, neck pain, and arthritis. So at this time, there's really no data to support that a small reduction in the use of opioids just in the first 72 hours has any impact on long-term use.

In addition, the current standard of care for postoperative pain management is based on a multimodal approach, which already includes the use of local anesthetics. At this time, it is unclear that EXPAREL offers any additional benefit to this approach, which was basically demonstrated in the second femoral nerve-block study.

To summarize the efficacy section of my talk, at this time we have two pivotal studies that did not meet their primary efficacy endpoint of AUC of pain intensity scores in the first 72 postoperative hours. Study 322 in the intercostal nerve block likely failed due to administration of EXPAREL into a highly vascular compartment, which possibly led to rapid absorption

of the drug prior to its ability to exert its local effect. Study 326, which was the second femoral nerve-block study, failed to demonstrate any benefit of femoral nerve block with EXPAREL over administration of bupivacaine via the posterior capsule.

We also have two pivotal studies that met their primary efficacy endpoints. Although study 323, which was the first femoral nerve-block study, demonstrated statistical significance in the AUC of pain intensity scores in the first 72 hours, as I previously discussed, the overall differences in pain scores were approximately 1 to 2 points, which questions the clinical relevance of this data. In addition, the study did not adequately characterize the safety profile of EXPAREL via femoral nerve block due to its truncated monitoring period and incomplete safety assessments.

In addition, since the literature data suggests that any amount of opioid in the first 7 postoperative days may be associated with prolonged opioid use, it can be concluded that none of the

pivotal studies were able to demonstrate significantly meaningful opioid sparing since almost all subjects in all studies still require significant amount of opioids in the first 72 hours.

At this point, we will switch gears and discuss the safety findings in more details, but before I do that, Dr. Naraharisetti will discuss the pharmacokinetic data from the applicant's development program, which has direct implications on the safety profile of EXPAREL.

FDA Presentation - Suresh Naraharisetti

DR. NARAHARISETTI: Thank you, Dr. Bazini.

Good morning. My name is Suresh Naraharisetti. I'm going to talk about the pharmacokinetics of EXPAREL from wound infiltration and nerve-block studies. This is the overview of my presentation. First, I'll give a brief background of EXPAREL from its label, and in infiltration studies, I'll show the PK systemic exposure of EXPAREL from studies that supported NDA approval. And to compare the PK between EXPAREL

and immediate-release bupivacaine hydrochloride, I'll show the results from an infiltration study in which both drugs were administered as separate treatments.

For nerve-block studies, I will do the same, show the PK results of EXPAREL followed by comparison between EXPAREL and immediate-release bupivacaine hydrochloride in a nerve-block setting, and finally conclude the overall findings. I will be using capitalized bupivacaine for immediate-release bupivacaine hydrochloride in my presentation.

The approved EXPAREL label notes that the systemic plasma levels of bupivacaine following the administration of EXPAREL are not correlated with efficacy, however, the systemic levels of bupivacaine from EXPAREL have implications for its safety profile. It also notes the rate of systemic absorption of bupivacaine from EXPAREL is dependent upon total dose, the route, and the vascularity of administration site.

EXPAREL was approved for surgical procedures

in which the method of administration was perioperative local infiltration. It was recommended for hemorrhoidectomy at 266-milligram dose and bunionectomy at 106-milligram dose. Studies for these two procedures was submitted in the original NDA. In these two procedures, the PK population of EXPAREL consisted of 25 and 26 subjects, respectively. The PK findings I'll present during the next two slides.

This slide shows the PK profiles of EXPAREL in hemorrhoidectomy and bunionectomy. The top two figures show the present hemorrhoidectomy and the bottom show the present bunionectomy. The Y-axis represents bupivacaine concentrations and the X-axis the time after drug administration.

The top-left figure shows the mean PK profile of bupivacaine from EXPAREL 266 milligram in hemorrhoidectomy. This profile shows the systemic absorption of bupivacaine from EXPAREL when administered as infiltration is almost instantaneous. For these mean concentrations, the scatter of individual concentrations at each time

point after drug administration is plotted on the top-right figure. As can be noted, the bupivacaine concentrations are largely scattered.

Say for example, at 12 hour after EXPAREL administration the individual concentrations in patients ranged between 47 nanogram per mL to 1210 nanogram per mL. Similar scatter can be observed at later points till 60 hours. The bottom-left figure represents mean systemic PK profile of EXPAREL 106 milligram in bunionectomy. The scatter of individual concentrations is plotted on the bottom right figure. Overall, these two infiltration procedures show that the systemic absorption of bupivacaine from EXPAREL between the individuals is variable.

The absorbed PK parameters in hemorrhoidectomy and bunionectomy are shown in the table. Since the EXPAREL doses are different between these two procedures, the Cmax and the AUC infinity are calculated per milligram dose. The dose normalized Cmax in hemorrhoidectomy is approximately 2-fold higher compared to

bunionectomy, while the dose normalized area under the curve is similar between two procedures.

The individual time to maximum concentrations are presented in the figure. The Y-axis indicates number of subjects and the X-axis indicates observed Tmax value. The Tmax values in hemorrhoidectomy are shown in black solid bars, while bunionectomy in black bars with diagonal lines. It can be noted that Tmax values of EXPAREL in both procedures have a wide range; in hemorrhoidectomy, the range between 0.25 to 36 hours, while in bunionectomy, the range between 0.5 to 24 hours.

The bupivacaine from EXPAREL liposomes is released over a period of time. To compare the systemic exposure of bupivacaine from EXPAREL and bupivacaine in a known infiltration procedure, inguinal-hernia repair study was utilized. The study was a phase 2, double-blind, dose-escalation safety, efficacy, and PK study in which escalating single doses of EXPAREL were compared with a single 100-milligram dose of bupivacaine. Both studies

were administered via wound infiltration. Systemic PK was compared between EXPAREL 155 milligram and bupivacaine 100 milligram. EXPAREL 155 milligram dose was chosen since it was the closest dose to bupivacaine 100 milligram.

This slide shows the PK profile comparison between EXPAREL and bupivacaine. The top figure shows mean systemic concentration time profile for both drugs. The bupivacaine is shown in the black dotted line and EXPAREL in black solid line. It can be noted that the shape of the mean profile is different between the two drugs for the same procedure.

For the mean profile, the scatter of individual concentrations is plotted on the bottom two figures. As can be seen, for the bupivacaine on the right, the scatter of individual concentrations is larger in initial time points, while for EXPAREL the scatter appears to be larger at all time points, till 48 to 72 hours.

When the individual concentration range at a later time point, say 48 hours after drug

administration, was compared for bupivacaine, they ranged between 0.1 to 80 nanogram per mL in all 26 subjects, while for EXPAREL they ranged higher, between 17 to 253 nanogram per mL in 12 subjects. Although it is not shown here, similar variability in systemic concentrations were observed for other doses of EXPAREL in the study. Overall, the systemic release profile and the systemic exposure for EXPAREL is different compared to the bupivacaine in an infiltration procedure.

For the absorbed systemic concentrations in the previous slide, the individual Tmax is plotted in the figure. Again, the Y-axis indicates number of subjects and X-axis the Tmax value. EXPAREL is presented in the black solid box and bupivacaine in the box with diagonal lines. Similar to what was seen for EXPAREL in hemorrhoidectomy and bunionectomy procedures using infiltration, the Tmax range of EXPAREL in this procedure is also wide with a range of 0.5 to 24 hours, while for bupivacaine in the majority of subjects, the Tmax occurs before 1 hour with a range of 0.08 to 6

hours. When the median Tmax was compared between two drugs, it was 12 hour for EXPAREL and 0.5 for bupivacaine.

As presented earlier, the efficacy supplement for nerve-block indication was presented to the agency in 2014 and 2017. In the next few slides, I'll present the PK findings of EXPAREL in nerve-block studies.

Since the systemic PK of EXPAREL is dependent on the type of surgical procedure, anatomical site, and type of administration, the PK was required to be collected in block studies to understand the variability between the procedures and to determine the duration of systemic safety monitoring for bupivacaine. Four phase 3 nerve-block studies were conducted for EXPAREL. I will briefly go over how EXPAREL was administered in these studies.

In study 322, EXPAREL 266-milligram dose was divided into three equal parts of 88 milligram and was administered into 3 nerve segments shown. In study 323, EXPAREL was administered using

ultrasound guidance. Study 326 was a repeated femoral nerve-block study. In this study, EXPAREL was administered using ultrasound guidance.

As you heard from earlier presentations, it is noted that an additional 40-milligram bupivacaine was administered in the posterior capsule in all treatment groups before closure of prosthesis, so for EXPAREL 266-milligram treatment group, the total dose of bupivacaine becomes 306 milligram. In study 327, EXPAREL was administered using ultrasound guidance. Although PK was evaluated at different doses of EXPAREL, for comparison purposes, I will only discuss the PK findings from the highest dose, 266 milligram.

The mean systemic bupivacaine concentrations from EXPAREL between nerve-block procedures are shown in this figure. For the same 266-milligram dose, EXPAREL PK profile in different procedures varies. The profile with cross marks represents intercostal nerve block. In this procedure, the absorption of bupivacaine from EXPAREL appears almost instantaneous. The profile with squares

represent the brachial plexus nerve block.

Coming to two femoral nerve-block studies, the circles and triangles in the middle represent them. The triangles represent study 323 and circles represent study 326. The 40-milligram additional bupivacaine administered in the posterior capsule can be noticed as initial bump in the PK curve in study 326.

Usually from the mean systemic profiles in the femoral nerve-block studies, the time to maximum concentrations for EXPAREL appears beyond 80 hours. The individual Tmax frequency distribution is presented in the following slides. Overall, for the same dose, the systemic PK profiles of EXPAREL are different between procedures.

For the mean systemic profiles presented in the previous slide, the individual concentrations at each time point of sample collection is presented here. Femoral nerve-block studies are presented in the top two figures. Bupivacaine concentrations from EXPAREL are largely scattered

in individual subjects. For example, in study 326 shown on the top right at 108 hours, which is equal to 4.5 days after surgery, the individual concentrations of EXPAREL vary between 43 nanogram per mL to 1120 nanogram per mL. A similar scatter was observed at several time points once after drug administration. Several concentrations are beyond 1000 nanogram per mL in the study.

In the intercostal nerve block, which showed instantaneous absorption shown in the bottom left, similar scatter was observed till last time point of sample collection that is 72 hours. The maximum concentration observed in this study is 2090 nanogram per mL.

In yesterday's presentation, the applicant mentioned that local anesthetic system toxicity is associated with bupivacaine concentrations of more than 2000 nanogram per mL referenced in three articles. However, it should be noted that these articles from the literature have studied healthy volunteers with a sample size of 11 to 14 subjects.

Knudsen and co-workers state that the mean

maximum tolerated venous plasma concentration of bupivacaine is 2100 nanogram per mL, however, there were subjects that were having symptoms of toxicity at levels as low as 800 nanogram per mL.

Dr. Bazini will be presenting the local anesthetic systemic toxicity in the safety section of her presentation. Overall, the systemic absorption of bupivacaine in the individual subjects is variable in the nerve-block studies.

This figure shows the individual Tmax distribution in nerve-block studies. First, I will focus on femoral nerve-block studies. The Tmax of EXPAREL in femoral nerve-block studies is much delayed. Study 323 is shown in black horizontal bars and study 326 is in black solid bars. The median Tmax in study 323 is 80 hours with a range of 60 to 96 hours. The median Tmax in study 326 is 72 hours with a much wider range of 2.5 to 108 hours observed in different patients.

For the intercostal nerve block, which showed instantaneous absorption, the median Tmax occurs much earlier at 1 hour with a range of 0.5

to 48 hours. The brachial plexus nerve block shown in bars with black dots, the median Tmax is 48 hours with a range of 24 to 72 hours. Overall, the time to peak concentrations of EXPAREL varies widely with a range of 0.5 to 108 hours requiring a wide range of safety monitoring for bupivacaine between different nerve-block procedures.

This table shows the comparison of systemic PK parameters of EXPAREL between different nerve-block studies for 266-milligram dose. First, I'll focus on femoral nerve-block studies in columns 3 and 4.

In study 326, because of the administration of 40 milligram bupivacaine in the posterior capsule, the total dose becomes 306 milligram. Because of this difference in the total dose between studies, the PK parameter Cmax and AUC were calculated per milligram dose. When compared, the dose normalized in Cmax and AUC in study 326 is higher by 30 percent and 27 percent, respectively, compared to study 323.

Now I'll focus on all four studies.

Overall, between the nerve-block studies, the systemic exposure as measured by AUC and Cmax of the same dose varies. For example, I will present the differences in four points.

Number 1, approximately there was 48 percent difference in AUC infinity between study 322 and study 323 for the same 266-milligram dose.

Number 2, there was 90 percent difference in dose normalized AUC between study 322 and 326.

Number 3, there was 50 percent difference in dose normalized AUC between study 326 and study 327. There was 70 percent difference in Cmax between study 322 and study 327 for the same 266-milligram dose.

Now, to compare the systemic exposure between EXPAREL and bupivacaine in the nerve-block setting, the ankle block study for bunionectomy was utilized. The study was a phase 2 efficacy, safety, and PK study in which single escalating doses of EXPAREL were compared to single 125-milligram dose of bupivacaine. Study drugs were administered via ankle block. PK was compared

between EXPAREL 155 milligram and bupivacaine 125 milligram.

This slide shows the systemic PK profile comparison between EXPAREL and bupivacaine. The top figure shows the mean profiles. Bupivacaine is shown in the black dotted line and EXPAREL in the black solid line. Like infiltration study in inguinal-hernia repair, the shape of mean profile is also different between EXPAREL and bupivacaine in this nerve-block setting.

The individual variability in concentrations is shown in the bottom two figures. As like the inguinal-hernia repair using infiltration, for bupivacaine the scatter is larger in the initial time points, where for EXPAREL the scatter appears higher at all time points till 72 hours. Overall, whether it is a wound infiltration or nerve block, the systemic exposure and PK profiles between EXPAREL and bupivacaine differs.

In conclusion, the variability of systemic concentrations for EXPAREL appears greater compared to the drug bupivacaine. Scatter appears larger

for bupivacaine in the initial time points, while for EXPAREL at all time points. For the same procedure, EXPAREL has longer and variable Tmax and extended systemic exposure compared to bupivacaine. The Tmax of EXPAREL between nerve-block procedures varies between 0.5 to 108 hours. The maximum observed Tmax was 108 hours, which is equal to 4.5 days after surgery.

For different nerve-block studies for the same dose of EXPAREL, the systemic exposure is different. Hence, predicting plausible systemic exposure from one nerve-block procedure to another is not feasible for determining the duration of bupivacaine systemic safety monitoring. The PK findings from nerve-block studies are like infiltration studies in which the rate of systemic absorption of bupivacaine depends on dose, route, and type of administration and the vascularity of the administration site.

Now I will turn it over to Dr. Bazini for her further presentation. Thank you.

FDA Presentation - Alla Bazini

DR. BAZINI: Thank you, Dr. Naraharisetti.

Prior to my discussion of the safety findings, I would like to highlight an important concept of local anesthetic systemic toxicity or LAST. LAST was first described in the 1800s in association with cocaine. As new local anesthetics were developed, LAST continued to be a safety concern and appears to be related to elevated plasma levels of local anesthetics.

There are numerous described presentations of LAST that typically include either neurologic or cardiac manifestations, or both. The time course of the presentation is typically within 1 hour for the non-extended release local anesthetics. At this time, it is unclear whether the liposomal formulation of bupivacaine may impact that time course of LAST.

As I briefly touched upon this morning, there were numerous safety concerns in the 2014 supplement submission. Specifically, the applicant did not fully analyze Holter monitor data in the intercostal nerve-block study and the first femoral

nerve-block study. In addition, Holter monitoring was discontinued at 72 hours, which was before the mean Tmax of the study drug, and the neurologic questionnaire was also discontinued before the mean Tmax in the femoral nerve-block study.

Additionally, block onset and duration was not characterized in the femoral nerve block or nerve blocks in general. For instance, there were falls that only occurred in the EXPAREL arms and not the placebo arms. Furthermore, the 20-meter walk test, which was conducted with an assist device such as a cane or a walker, has low sensitivity and specificity to detect a motor block. Finally, given the large difference in the PK profiles observed and different anatomical sites, the applicant failed to provide adequate support for extrapolation of safety for all other nerve blocks.

In the next several slides, I will discuss how the applicant addressed these deficiencies. In 2017, the applicant resubmitted reanalyzed Holter monitor data through 72 hours and ECG data from

studies 322 and 323. The Division of Cardiovascular and Renal Products was consulted to review this data in addition to the cardiac data in the two new pivotal studies. The division concluded that there were no cardiac related safety concerns with the previous Holter monitor data in studies 322 and 323, however, this only reflects findings for the first 72 hours, which was before mean Tmax of EXPAREL.

Continuous cardiac monitoring was not done in studies 326 and 327, but rather ECG data was collected at prespecified time points and at times of prespecified adverse events. Based on the data available, no cardiac toxicity concerns in the two new studies were identified.

The two new studies also included a neurological questionnaire which was continued beyond Tmax in both studies. Although there were numerous multiple adverse events that could be neurological manifestations of LAST, there was no clear signal identified. However, there were multiple confounders, which include the surgical

procedures themselves and the concomitant perioperative medications, which made the interpretation of the etiology of the neurological adverse events very difficult.

To address the block characterization deficiency, the applicant performed sensory and motor assessments through 120 hours. Sensory assessments included cold, light touch, and pinprick in both studies. Motor assessments included knee flexion and extension in the femoral nerve-block study and elbow flexion, thumb abduction and adduction, and thumb opposition in the brachial plexus nerve-block study.

There were several subjects who had persistent sensory deficits at 120 hours in study 326, the second femoral nerve-block study. The number of subjects with persistent sensory deficits increased from placebo group to the EXPAREL 133-milligram group and further increased to the EXPAREL 266-milligram group.

This table summarizes the median time to loss of sensation in the second femoral nerve-block

study. Subjects in the EXPAREL arms had loss to sensation at approximately 6 hours, where subjects in the placebo arm had median time to loss at 72 hours. However, the confidence intervals for the placebo group are extremely wide with some subjects also having loss at approximately 6 hours.

As you can see, there's a large difference between the mean Tmax of EXPAREL at 72 hours and the median time to loss of sensation at 6 hours. Since the time to loss of sensation can be correlated with local drug efficacy, this supports the notion that local drug efficacy doesn't correlate with systemic drug levels.

This table summarizes time to loss of motor function in the same study. It should be noted that subjects at the Belgian site, which had 50 percent of the study population, were immobilized for the first 2 to 3 postoperative days, which is a common surgical practice at this site. Due to this immobilization, no motor assessments were performed in these subjects. Since the data for onset of motor loss from about

half of the study population is missing, the motor block onset was not fully characterized.

What this table represents is the time course of motor function return in the knee in all study groups in the same study. I point your attention to the red box here, and as you can see, the number of subjects who did not have motor function return at 120 hours was similar in all study groups. This supports the hypothesis that post-surgical changes may be the cause of delayed function in the total knee arthroplasty patients.

Since both placebo and EXPAREL arms had similar rates of failure to return to baseline motor function, one would expect the same rate of falls between the groups, however, this did not happen. As you can see, in both femoral nerve-block studies, falls were only present in the EXPAREL arms.

Also notable is that in study 323, each of the subjects who fell was able to pass a 20-meter walk test at three prespecified time points and had a physician who was satisfied with the subjects'

return of sensory motor function at 72 hours. These findings suggest that EXPAREL was causal in the falls and that success of the 20-meter walk test does not correlate with absence of fall risk.

Although it is possible that either generalized postoperative motor weakness or the femoral nerve block itself may have contributed to this increased incidence of falls in the treatment groups, in the absence of an active control arm with bupivacaine administered in the same manner it is impossible to make such a conclusion. Therefore, at this time, we must conclude that EXPAREL may lead to increased incidence of falls.

This table summarizes the median time to loss in the brachial plexus nerve-block study. Subjects in the EXPAREL arm had loss to sensation at approximately 6 hours, whereas subjects in the placebo arm had median time to loss at 72 hours. Similarly to the femoral nerve-block study, there's a large difference in the mean Tmax of EXPAREL, which was at 48 hours, and the median time to loss of sensation at 6 hours. Again, this supports the

notion that local drug efficacy doesn't correlate with systemic drug levels.

This table represents the median time to motor loss in the same study, which basically mirrors the sensory loss pattern we saw in the previous slide. As opposed to the femoral nerve-block study in study 327, most subjects in the EXPAREL had resolution of the motor block 542 hours.

To summarize, the two new studies in the femoral nerve block and brachial plexus block included focused sensory and motor function exams through Tmax and until resolution of the nerve block. Unfortunately, since 50 percent of the subjects in the femoral nerve block had missing motor block assessments in the first 2-plus postoperative days, the onset of motor block was not fully characterized in this study. On the contrary, it appears that the sensory and motor blocks were well characterized in study 327.

Overall, the data show significant variability and block onset and duration depending

on the site of injection. Onset of sensory and motor loss did not correlate to Tmax. And finally, falls were only seen in the EXPAREL arms in the femoral nerve-block study. It is unclear whether prolonged femoral nerve-block-induced quadricep weakness from any local anesthetic would result in an increased incidence of falls or whether EXPAREL further increases this risk because these studies did not have an active comparator arm of bupivacaine given via femoral nerve block. An additional study where EXPAREL is compared to bupivacaine via femoral nerve block would help to differentiate such a risk.

The last section of my presentation today will focus on local anesthetic systemic toxicity or LAST. The Division of Pharmacovigilance searched the FAERS database and medical literature to determine if there is evidence of delayed onset of LAST with EXPAREL or the non-extended release injectable local anesthetic. All local anesthetic labelings include varying language describing the signs and symptoms of LAST or include things like

systemic toxicity as an adverse event. However, none of the labels currently describe the timing to onset or signs and symptoms.

The FAERS search included six years for EXPAREL since it was approved in October 2011. The FAERS search for the non-extended release local anesthetics included the past 11 years in an effort to retrieve the most up to date prescribing practices. Of note, DPV defined rapid onset of LAST as occurring less than an hour and delayed onset LAST as occurring greater than an hour to 96 hours.

A little bit about drug use, in 2015, approximately 164 million total eaches of local anesthetic injectable products were sold from manufacturers. Eaches refer to the number of vials, ampules, syringes, cartridges, IV bags or cassettes of products shipped in a unit.

As you can see in this graph, lidocaine makes up the largest proportion of these sales, the two lines at the top, while EXPAREL makes up less than 1 percent of the eaches, which is the very

bottom dotted line. If you look at the bupivacaine products combined, there were approximately 20 million eaches sold with EXPAREL sales equaling less than 1 million or 4 percent of the bupivacaine sales.

The results of the DPV review are depicted on this slide. Before I go over these results, I would like to mention that FAERS and literature case reports are a collection of case-level data without full enumeration of all events and exposures. Although the previous slide showed the estimated U.S. sales of EXPAREL is less than other local anesthetics, the results shown on this slide are not adjusted for sales or actual product use.

There are various factors that affect whether an adverse event will be spontaneously reported, including time on the market and publicity of a product or an event. Considering these and other limitations of spontaneous reporting systems, we present these FAERS and literature results to provide a description of the reported cases and not a quantitative comparison

amongst the products.

There were a total of 111 cases of LAST with 39 attributed to EXPAREL versus 72 attributed to other local anesthetics. The number of cases of rapid onset of LAST and delayed LAST was similar with EXPAREL, whereas most cases of LAST with other local anesthetics were rapid in onset. There was also a total of 8 fatalities, 5 of which were attributed to EXPAREL. Clinical manifestations involve signs and symptoms of cardiovascular or central nervous system toxicity, and lipid emulsion was used in some instances for treatment.

Our overall conclusions regarding LAST is that it can occur across all injectable local anesthetic classes with a variable time to onset and presentation. Clinical symptoms were generally similar among EXPAREL and other local anesthetics. Timing of presentation is also variable and may depend on mode of administration, dose, and patient related factors.

In a review of published cases of LAST from 1979 to 2009, Di Gregorio and colleagues wrote, and

I quote, "Thresholds for entertaining this diagnosis should be lowered and toxicity should be considered a higher probability when the patient is in a group considered to be at higher risk for local anesthetic toxicity; for example, preexisting cardiac, pulmonary, metabolic, or neurologic disease, or at extremes of age." Unquote.

As mentioned by Dr. Naraharisetti, although there are studies indicating that the mean maximum tolerated venous concentration of bupivacaine is around 2000 nanograms per mL in healthy volunteers, this may not be applicable to most surgical patients, in particular, those who have underlying risk factors I just mentioned.

The current language regarding LAST in local anesthetic labels is variable, and none mention the risk of delayed LAST. The FDA is continuing to monitor for reports of delayed onset LAST and will determine if regulatory action is indicated.

To summarize our safety evaluation, I will once again reiterate the safety of EXPAREL is based on local drug effects and the total systemic

bupivacaine exposure. The data submitted to date, which was presented earlier by Dr. Naraharisetti, demonstrate a great variability in the systemic exposure of EXPAREL based on the site of injection and administration technique. Given this variability, it is impossible to predict what systemic exposure may be at sites of administration that have not been studied.

The applicant has not provided a rationale to support extrapolation of the pharmacokinetic data to other commonly performed nerve blocks. In addition, as we saw in the brachial plexus study, the 266-milligram dose of EXPAREL is not an ideal dose for all nerve blocks. Since many physicians will often administer the highest label dose, absence of predetermined dosing guidelines specific for nerve blocks may lead to overdosing and increase the risk and possibility of local anesthetic systemic toxicity. Finally, the risk of delayed LAST is still uncertain and requires further monitoring.

This concludes my presentation this morning.

I thank you for listening, and I will open it up to questions.

Clarifying Questions

DR. McCANN: Are there any clarifying questions for the FDA or the speaker? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. This is for Dr. Bazini. With regard to the 8 fatalities, do you have ages for those, from the LAST data?

DR. BAZINI: I believe we do, although I don't have that right now. We could get those to you.

DR. HIGGINS: Thank you.

DR. BAZINI: There we go. One of my colleagues is going to present that.

MS. CASCIO: I'm Laurelle Cascio. I'm a safety evaluator in DPV. I have for those deaths the ages. One was an 88-year-old female; another was a 60-year-old male; another was a 50-year-old female patient. There was another case with a

66-year-old male; and an 87-year-old female. There was one case that didn't report the age.

DR. HIGGINS: Is it possible to break that out by EXPAREL versus the other LAs?

MS. CASCIO: Yes. For EXPAREL, it was the 60 year old; the 50 year old; 66 year old; and 87 year old.

DR. HIGGINS: Thank you.

MS. CASCIO: Sure.

DR. McCANN: Any other questions? Dr. Shoben?

DR. SHOBEN: This is for Dr. Meaker. I was wondering about the imputation of this worse observation carried forward and if the data you presented was shown using that imputation and if you had the non-imputed data.

MS. MEAKER: The results I showed were using the imputed data because that was the primary planned analyses. We do have the unimputed data, but I elected not to show those results here. It's consistent. There are no issues that came up with them.

DR. McCANN: Dr. Craig?

DR. CRAIG: Thank you. Just a clarifying question on those fatalities. Do you have a sense of -- I'm trying to get a sense of route of administration. Was that noted? And just a follow-up question to that would be was that from FAERS data? Where was that data obtained from, spontaneous reports from the company or was it reported to FDA?

MS. CASCIO: This is Laurelle Cascio. They were all from FAERS data. Actually, there was also one -- there were 7 from FAERS and one from literature. As far as route of administration, if you want I can collect the data. It's holding up the question, but -- I'm reading through narratives to find it. I think we'll get back to you, and I'll collect the data.

DR. McCANN: Dr. Litman?

DR. LITMAN: Thanks. I can't imagine you have this kind of data on the fatalities, but do you know if any of them were resistant to rescue with intralipid? I mean, normally with bupivacaine

cardiotoxicity, you would try an intralipid rescue, which may or may not work. But I was just curious if there was any indication that it failed for some reason with EXPAREL.

DR. HERTZ: I think we're taking note of all those questions, and I think we'll give the team a chance to check through the narratives.

DR. LITMAN: Sure. Thanks.

DR. McCANN: I have a follow-up question to the same thing. I think everybody's curious about these fatalities. Do we have any idea what the doses were used? Were they the 133 or the 266? And were any of the patients -- were they all in-hospital deaths or had any of the patients been discharged?

DR. HERTZ: Are there any more questions about LAST deaths, so that we can just make sure they're checking everything for the answers?

DR. McCANN: Dr. Porter?

DR. PORTER: Laura Porter. I was wondering, yesterday the company presented information on deaths and their numbers are different than what

was presented by you all. I was wondering what the correlation is or if there is any correlation for the deaths reported by the company. I can give you the slide number, CO-69. It's in the handout.

DR. HERTZ: Those were clinical studies, and these that we're talking about now are in postmarketing, our adverse event reporting system.

DR. PORTER: So they're additional then.

DR. HERTZ: Yes. They're not from controlled studies. That's why it's so hard to get the details put together.

DR. PORTER: Okay. Thank you.

DR. McCANN: Dr. Zacharoff?

DR. ZACHAROFF: Kevin Zacharoff. Dr. Bazini, in slide number 98, the results of the DPV review where the fatalities are mentioned, it's also mentioned that there were 24 cases of recorded suspicion or confirmed inadvertent intravascular administration, one case with EXPAREL. And I was wondering if we know what the outcome of those were. Maybe we can add that to the list.

DR. BAZINI: Again, I will defer to my DPV

colleagues. I'm not sure if they have the details of that specific case.

DR. HERTZ: So let's focus on those slides about the postmarketing data for a moment. For the committee, if you guys have any other elements of questions, it's just easier for them, I think, if they go through it once. Anybody else?

(No response.)

DR. HERTZ: Okay. So when they have a chance to put that together, we'll give them a seat and let them go through that all with you.

DR. McCANN: Dr. Galinkin?

DR. GALINKIN: I have two questions. One is, do we have any data on peak bupivacaine levels with epidurals and continuous nerve catheters so that we can have a comparison basis for the peak bupivacaine levels that occur at 72 hours with EXPAREL?

DR. HERTZ: No. We don't from the clinical studies because, again --

DR. GALINKIN: Or does the company?

DR. HERTZ: General data?

DR. GALINKIN: General data, because that seems like an exposure to a higher level than -- higher plasma level for a longer period of time. And I'm just curious if we've seen that with other anesthetics.

DR. HERTZ: I'm clearly not an anesthesiologist, but the dose for epidural is quite a bit lower. I see the anesthesiologists shaking their head. I don't think we have any information from systematic approach to those methods of approval. The use of catheters is not labeled, so we don't have any systematic collection of that.

DR. GALINKIN: I'm talking about nerve-block catheters. There's not a lot of places where we send people home with larger doses of local anesthetics. So from a comparative basis, these peaks at home I think are the concerning safety features from our perspective, especially with the data that you're suggesting that are problems with a 1000 or less than 1000 nanogram per milliliter blood level causing toxicity with it, and you're

sending patients home with a higher level of toxicity potentially. That would be our concern, is the data from nerve catheters, which sounds like the company had because I heard them mumble behind us.

DR. HERTZ: Okay. But just remember, we don't have any evidence that EXPAREL is comparable for efficacy for that either. It's not even beating regular bupivacaine.

DR. GALINKIN: Oh, I'm not talking about efficacy. I'm talking purely about safety.

DR. HERTZ: Purely for safety.

DR. GALINKIN: I mean, obviously that to me seems like the primary concern. The efficacy is almost secondary to safety at this point. Right?

The second question that's specific for Alla, on slide 49 from the FDA, the nine studies that failed to demonstrate clinical or a statistical difference between EXPAREL and bupivacaine, were those designed as noninferiority equivalents or were they designed to have a difference -- were they powered, I'm sorry, for any

of those?

MR. PETULLO: David Petullo. I was actually the stat reviewer for some of those studies. They were superiority studies.

DR. McCANN: Dr. Terman?

DR. TERMAN: I was also perseverating on this non-imputed versus imputed pain score question. And particularly for 327, the brachial plexus, I would really like to see that data if it's available, the non-imputed, at some point during the day. It strikes me that could certainly raise the pain scores on the placebo patients that are getting quite a bit of opiate.

MS. MEAKER: I don't have it currently in the slides. I can provide that after the lunch break.

DR. TERMAN: Great.

MS. MEAKER: Okay.

DR. TERMAN: The second question I have --

MR. PETULLO: Can I make one clarifying comment here?

DR. TERMAN: Sure.

MR. PETULLO: We keep using the word "imputed." These were when a patient took rescue medication. We measured their pain score before they took the rescue medication and used that for a certain window based on what the rescue medication was. So they weren't missing values.

DR. TERMAN: Right. So --

DR. HERTZ: This is a very common approach that we take. If you're going to have a placebo or any type of superiority trial, and you're going to offer rescue -- because to have somebody have unmanaged pain for some number of hours typically leads to, one, ethics problems; but, two, dropping out of studies so that they can get pain relief -- it's typical for us to do that, because otherwise, if we're measuring the scores after rescue, it doesn't reflect the treatment that's been assigned.

So for both placebo and for active, if we have -- like for instance with this where we've got a long evaluation period and a short-acting rescue, that's a very common method to minimize the impact

of rescue on the actual scores. So we can get you the data, but the data are going to reflect the pain scores after the rescue. So we'll get it, but I just want you to understand that this was not any kind of unusual thing. This is a very normal approach to analysis in analgesic studies, but we will get it.

DR. TERMAN: Okay. I don't doubt that it's common, but it's nice -- so clinically, I'm interested in how much pain medicine they took, and that's here, but I'm also interested in how much pain they have despite that treatment.

The second question I have is -- and this may in some ways go back to the previous acceptance for an indication for infiltration, but I think it's even more important for nerve blocks. And that is, is there any requirement for more local toxicity analysis?

Now that there's been a request for nerve-block indication, there's definitely going to be intravascular, either arterial or venous, injections of this medication, and I'm just curious

what is asked for in terms of the danger of an organ. For instance, if I give a bolus into the venous system, am I going to cause ischemia in the lung for instance, if it makes it to the lung, or if it's into the artery going to the brain, for instance, on my interscalene block, am I going to cause a stroke.

What sorts of data is requested there?

DR. HERTZ: So the sponsor presented the nonclinical studies, and that's usually what we ask for before nerve blocks and I think before epidural studies are done, that they actually do an intentional intravascular injection of species relevant quantity of the product that's representative of either the to-be-marketed or very close formulation so that we can look for anything that would be associated with occlusion, distal problems, collection in the lungs, any of that, and we heard those results yesterday. Then of course during clinical trials, we monitor but luckily we don't see that. But usually the classic is to do the nonclinical studies before the actual clinical.

DR. TERMAN: Okay.

DR. McCANN: If we have time, the sponsor I believe has a slide relating to that because that was something that we questioned yesterday.

DR. TERMAN: Okay.

DR. McCANN: So we'll see if we have time.

Dr. Porter?

DR. PORTER: The use of the local anesthetics, EXPAREL, does that lessen the amount of general anesthesia that is necessary?

DR. HERTZ: These studies did not look at that. These are all about postoperative pain, so we don't have information on that, so not on the table.

DR. PORTER: Okay.

DR. McCANN: Dr. Zacharoff?

DR. ZACHAROFF: Kevin Zacharoff. This question is for Dr. Bazini referring to slide 59, just for clarification because I use this phrase myself. I hear other people use it. And I'd like to know what the hard, fast definition of opioid sparing is, because very often I talk about it in

terms of amount of medication used as opposed to clinical reduction in pain scores and things like that.

So the last bullet says, "No studies were conducted, to date, demonstrate clinically meaningful opioid sparing," which to me implies possibly related to pain score as opposed to amount of medication used with majority of subjects still requiring a significant amount of postoperative opioids. I would almost never expect the use of a local anesthetic to zero out the need for opioid supplementation, although I have seen it. But I don't consider that to be the definition of opioid sparing.

DR. HERTZ: Right. This is Sharon Hertz with an answer because it's actually a very big question that we're working on, and we're probably going to write guidance on that.

Historically, when sponsors have come in and sought an opioid-sparing claim, we ask for some sign that it's going to be clinically relevant. What is the purpose of the opioid sparing? Is it

specifically intended to reduce post-opioid associated adverse events? If that's the case, then the study is powered for a particular adverse event. For instance, one thing that's been very appealing is postoperative nausea and vomiting.

So if we have a specific endpoint that the sponsor is interested in addressing, that becomes clear. When it's just a general sense of opioid sparing, then we go from the absolute, which would be, yeah, it would be great if there was no opioid use but that is a very high bar, to figuring out what is meaningful.

For instance, is the difference between 90 and 120 milligrams of morphine over 3 days useful somehow, and if it's enough of a difference to impact reduced ileus or easier getting patients up to move? Whatever it is, then we can focus on that. But when it's just a difference, that's where we struggle because it's potentially true but irrelevant.

In a sense, you can see differences that clearly raise a question about the value, like the

difference of 10 milligrams per day when someone's taking 30 or 40 milligrams per day. But what if that was a difference of 20 milligrams per day? Well, I don't know. Or 30 milligrams per day? So these shades of gray have to be sorted out, and that's why we often try to focus on something a little bit more fixed.

Now, in terms of the opioid crisis and how one can impact that with opioid-sparing methodologies, we're very interested, obviously. Some of the easiest things are to use non-opioid medications, period. Post-third molar extraction, NSAIDs are terrific. I don't know why we ever switched to opioids. Right? But in a complex setting like this, it's much more difficult. You can't just --

So we're working on that. And the reason why I have highlighted that in my comments is because I would like to hear from you-all what you think clinically relevant differences would look like to help us interpret the data. So while we have a sense of what it isn't, it's much harder to

define what it is.

DR. McCANN: Dr. Gulur?

DR. GULUR: Thank you, Dr. McCann.

I have a question regarding intraneural injections. Was that something, Dr. Bazini, that you had looked at, looked into, and is there any data on differences where a depot formulation is intraneurally injected versus regular local anesthetic, and is there any local neurological tissue damage to the nerve because of it?

DR. BAZINI: I am not aware of data like this. Like I said, I think Dr. Sharon already pointed out that the sponsor had done a couple of studies where they were injecting intravascularly, but I am not aware of any intraneural injections.

DR. GULUR: Thank you.

DR. McCANN: Are there any more questions for the FDA other than the clarifying information that we're probably going to get after the break?

(No response.)

DR. McCANN: Dr. Hertz, do we have enough time for them to present two or three more

clarifying slides?

DR. HERTZ: Yes.

DR. McCANN: Thank you.

DR. SCRANTON: Thank you very much. So we'll start with the question with regards to the additional animal studies that we conducted. This goes back many years, as Dr. Hertz spoke, that this has been part of our filing for the nerve-block studies. What I showed yesterday was just the IV study, and I will show you now all the dog studies that we've done as part of our filing.

Here in total, it equaled 80 dogs. What I showed you yesterday was just the IV at that one dose. We looked at a variety of doses even higher than that from intravascular or intra-arterial administration of the drug, and you can see, we would expect if we had any thromboembolic events, that would occur around 2 days. That's when we sacrificed a number of the animals, and then we also looked at 15 days post.

Just to give you a very high-level summary of that, when we looked across all the tissues for

all dogs, there was no test article related microscopic findings in any organ that was tested on either day 2 or day 15. I'll just show you the question. Whether it was intra-arterial or intravenous, these are all the lists of tissue organs that were evaluated. So again, no evidence of a thromboembolic event at doses at 4.5 or 9 milligrams given either intravenously or intra-arterially, and we had comparisons of both saline and bupivacaine as comparisons.

With regard to the deaths, that's very important to us at this era. We have a very extensive and comprehensive program for drug safety surveillance. What we have observed is it's very difficult. There is no defined definition of LAST. Even when events are reported as cardiovascular or neurologic, they still may be a result from the underlying comorbidity of patients having surgery or the surgery itself.

We can bring up the four cases from what you just showed where we did get additional information from the FDA's database. This is part of our

global surveillance program that we've been doing since the launch of the drug. These are the four cases where we're able to look at the actual case, and you can see there are numerous confounders, as reported, when you read the case reports of patients having other very sick patients; for example, the woman who was 87 years of age. All of that was just pointing out that you can glean some information from the case reports.

Oftentimes, the healthcare provider who is doing the report will say specifically where they felt that a case was LAST or not and not definitive, however, this is what was reported in those four cases. This is something, again, that we monitor on a daily basis.

Finally, I just wanted to point to the one discussion with regards to our prior studies in the nerve-block studies. All of our phase 2 studies, they were phase 2 studies. They weren't powered on superiority because of the sample size. And I think it's important to note, being an outcomes researcher, a patient-reported outcomes researcher,

we all know that bupivacaine is an efficacious drug, but yet even bupivacaine, known to be efficacious -- if you can look at this publication -- 50 percent of the trials with bupivacaine against placebo control and joint arthroplasty had been demonstrated not to be successful. Because we know that we have a subjective outcome and that patients need the rescue, we can't allow patients to experience pain in our trials. So these are the challenges for all of us who do this type of research.

In our phase 3 active-controlled comparator trials that were mentioned today, some of those, study 311 from the TKA study, we learned from that study. We applied that to our 331 study, which was an active comparator for infiltration demonstrating significant reduction in both pain and opioid use. Similar, we did a breast study that was installation.

We have now moved towards an appropriate infiltration technique, including PEC 1/PEC 2, and now there's been a consensus document published on

that, and subsequently we're going to do some follow-on studies. So we've learned a lot from what we've done before. We've applied them to our follow-on projects and have demonstrated significant benefit for patients. So thank you for the time.

DR. HERTZ: Just to comment, though, this is why when we have products like that, we repeatedly request that studies be designed so we can detect these differences. And to have a placebo and an active comparator in addition to EXPAREL would have really silenced a lot of the questions that arise from only doing placebo-controlled studies.

DR. SCRANTON: One additional question I forgot, we can bring up the comparator data, a continuous brachial plexus nerve block and the PK levels for that. One of the challenges -- and I agree with you, Dr. Hertz -- is finding the appropriate comparator. As we're giving a single injection of EXPAREL that lasts for 72 hours, we could compare an active comparator against a brachial plexus block.

DR. HERTZ: Again, we don't know that EXPAREL lasts for 72 hours independent of bupivacaine. We have outcome data for AUC for 72 hours, but that's not necessarily what we find in the pain curves. So these are the problems with the placebo-controlled studies, and we don't yet know for a fact that there is an added duration effect. That's the point.

DR. SCRANTON: I understand. But the question that was raised with regards to safety and toxic exposures from the use of peripheral nerve blocks, this was just a demonstration from brachial plexus that for the first 24 hours, you're consistently exceeding levels higher than we observed in our brachial plexus study. And you're absolutely right.

As we looked at all the physicians out there that are looking at the use of EXPAREL in a variety of nerve blocks that already have been done outside of our control, they had demonstrated against continuous bupivacaine. This slide is just demonstrating where they assess pain, and green

would be favored EXPAREL. Yellow perhaps neutral, in some cases, against a continuous nerve block, there would be no expectation that it would be a difference in opioid use, but you can see Vandepitte, Rice, Mehran and thoracotomies. Most recently, just last week, was a study done in children as young as the age of 6 who had a palatal block demonstrating benefits in pain and actually returned to oral consumption.

So you're absolutely right. I think for efficacy, those studies are being done. What we were demonstrating was the safety, and there finding the appropriate active comparator would be challenging. And I'm confident at the end, we were able to demonstrate that we were safe to placebo with regards to any neurologic or cardiovascular side effects.

DR. McCANN: I believe we have one question. Dr. Litman?

DR. LITMAN: Thanks. Can you bring up that -- Dr. Scranton, sorry, before you walk away -- forest plot you just showed, where you were

trying to make the point that even bupivacaine fails?

DR. SCRANTON: Yes, sir?

DR. LITMAN: You said that 50 percent of those studies showed that it didn't work? That's what I thought I heard.

DR. SCRANTON: This was the publication here. In general, if you look even across all pain trials for pain studies, the success is around 50 percent. I'm sorry. Here it is.

DR. LITMAN: I'm not seeing anywhere close to 50 percent. I just wanted to clarify that. Almost all of the studies showed that bupivacaine worked. I guess maybe there were a couple patients in one, two, three, four studies where it approached 95 percent. I just wanted to clarify that.

DR. SCRANTON: Okay. I agree, but several studies known to be efficacious against bupivacaine crossed the boundary here. And this is known for all pain drugs, not just local anesthetics.

DR. LITMAN: I agree, but that slide

certainly doesn't insuate 50 percent of them didn't work. But the other important question I had for you is have you taken any of the dog studies and injected them intravenously until they had cardiac arrest?

DR. SCRANTON: The highest dose that we went up to was 9 milligrams, and in that case, we didn't have arrest of all the dogs. There could be a higher dose, but that is the highest level we went. And the dogs were in significant distress at that time and we had to use a much lower dose of bupivacaine because that was leading to cardiac arrest in those animals.

DR. LITMAN: Okay. I'm just concerned about a couple things. One, I want to make sure that when you take comparators between regular bupivacaine and EXPAREL, and you inject them intravenously into an animal model, they'll be comparable with the amount that cause cardiac arrest. That's one. Number two, I want to see that in bupivacaine animals, not EXPAREL, that can be rescued with intralipid, that that's also

comparable with EXPAREL

DR. SCRANTON: Thank you.

DR. CONNER: If I may speak to this real quick. This is Jason Conner, the statistical consultant. The idea, of the 8 trials shown here, that 4 have confidence intervals that overlap zero indicating no effect. The first 4, 6, and 8th, and in fact, the 6th trial, Ritter [indiscernible] here, was the largest trial of 200 patients, and you can see the effect in absolutely zero, so even the biggest trial.

DR. LITMAN: Okay.

DR. CONNER: Many of these are in the right direction just like many of the studies that our primary endpoint didn't hit the right direction, but the confidence intervals still overlap one due to some of the noise and the struggles surrounding these trials.

DR. LITMAN: Thank you.

DR. CONNER: Thank you.

DR. McCANN: Dr. Terman?

DR. TERMAN: Thank you. Greg Terman. The

9 milligrams that you gave, what kind of volume is that? I apologize for not knowing that.

DR. SCRANTON: This was the dose for giving a dose -- we had to change the concentration based on the milligrams per mL here on the right, dose concentration milligram per mL, to achieve an equivalent dose level over milligram per kilogram. So if I were to extrapolate, for example, 4.5 milligram per kilogram, that would approximate, in a 60-kilogram adult, a full dose of our vial of EXPAREL, 266 milligrams.

DR. TERMAN: Sorry. So what milliliters would that be given?

DR. SCRANTON: So if this was 7 --

DR. TERMAN: Because I'm worried about blocking blood flow to wherever the liposomes go. So if you give the volume, are you going to block blood flow to the lung or to the brain? That's what I'd be worried about. So if I'm giving a nerve block, there's going to be a certain amount of times where I'm going to get that intravascular or intra-arterial, so I'm just curious whether the

volumes are big or small in comparison to what might happen in a clinical situation.

DR. SCRANTON: In the dog -- so if we're dealing with a 20- to 30-kilo mongrel dog, if we're doing 9 per kilo, which is really an enormous dose, you're somewhere there between 13 and 27 cc's, would be the maximum cc's you'd do it. And again, in a person, it would be 20 cc's of the EXPAREL to get 266 milligrams.

DR. TERMAN: Okay. Do you know what happens as an effect of pH to the liposome? Do you know whether the liposomes break down as a function of pH? Let's say it's in an artery and you get ischemia of some sort, do you know what happens to the liposomes?

DR. SCRANTON: We looked at physiological pH. Only at extremes pH did we see that it has some impact on the release of the drug. As we know, bupivacaine doesn't work as well, and in fact, the tissue -- but when it gets into -- if you inject it intravascularly, it's the other cytokines in the blood and change in temperature that is

resulting in that first release, about 30 percent of free bupivacaine. Otherwise than that, we don't see any other effect at the local tissue level as far as release, based on pH.

We do have the animal for toxicity -- that was the other question that was raised -- as far as neurotox. We do have that data as well. We've done comprehensive studies as part of our initial filing, again, going back from our original NDA. But if possible, Dr. Byram can share the most recent data of looking at neurotox data from the application of EXPAREL.

DR. BYRAM: Good morning. My name is Susanna Byram. I'm an assistant professor at Loyola University in anesthesia and critical care medicine. Also, I'm a basic scientist, and I do nerve injury and repair research for the last 20 years as a basic scientist in animal models. In my experience using EXPAREL in my lab, as well as just the review of some other laboratories that have looked at EXPAREL in preclinical models, there's been no evidence of toxicity to nerves.

I'm particularly interested in local anesthetic toxicity to at-risk nerves, so in my lab I do an injury to my nerve first, and then I've used one of seven different local anesthetics. And as you can see here, I do see toxicity with some of the local anesthetics, but EXPAREL I did not.

I've done this in a couple of different models. This was an axotomy model where it's a complete transection, and then I've also done it in a crush-injury model where you can also follow for functional recovery, which is really important clinically. So if a nerve gets injured, you can follow it functionally to see if that nerve can recover.

Again, I show here that most of the local anesthetics did not delay functional recovery, but EXPAREL did not in that case. So I feel like perhaps something with this formulation, this slow release of bupivacaine may afford some bit of safety to the toxicity that we normally can see with local anesthetics.

DR. McCANN: Dr. Gulur?

DR. GULUR: Thank you. Actually, my question, you had mentioned you have intra-neural data.

DR. BYRAM: My data isn't intra-neural. For my data, it was local anesthetics onto either an injured nerve, crushed or axotomized. If you can bring up the charts that I had. There are a couple of other studies from other investigators that have looked at EXPAREL, and I believe it's the third one down where they have looked at a pig sciatic nerve. They did do perineural and intra-neural injection of EXPAREL, and they didn't see -- they followed both sensory and motor deficits. They didn't see any persistent sensory motor deficits, no changes in their nerve fibers, the density or the myelin. So ultimately they didn't see any difference.

DR. GULUR: And what volume were they using in these pigs, and how many pigs?

DR. BYRAM: I don't know that. I'd have to figure that out.

DR. GULUR: Thank you.

DR. McCANN: Are there any more questions?

(No response.)

DR. McCANN: If not, we'll break for 20 minutes, which will take us to 10:36. Just to remind you, there will be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. Thank you.

(Whereupon, at 10:16 a.m., a recess was taken.)

DR. McCANN: Welcome back. We have just enough time for some information from the FDA and then time for some clarifying questions.

DR. CASCIO: Hi. This is Laurelle Cascio from DPV. In response to some of your questions, regarding one case of the inadvertent intravascular administration of EXPAREL, the age was unknown. It was a female. She received 266 milligrams of EXPAREL with an unknown route for post-op analgesia. The patient experienced mild clonus in the PACU. She also received intralipids, and the case was categorized as other serious by the reporter.

In response to the question about the

EXPAREL deaths, I've already given the ages. As far as route, two of the cases reported infiltration; two cases did not report the route; and the remaining case reported an IM into the deep soft tissue in the surgical site. As far as the doses go, one case reported 266 milligrams of EXPAREL; two cases reported 20 mLs; one case reported one vial; and the remaining case did not report a dose.

As far as lipid rescue medication; three cases did not report whether the patient received lipid rescue or not; one case specifically mentioned they did not receive lipid rescue; and one case did receipt lipid rescue, but the dose was not reported. And all deaths occurred while the patient was hospitalized.

DR. McCANN: Do we have any clarifying questions? I have a question. What is 20 mLs for a standard undiluted drug? Do you know?

DR. BAZINI: 266.

DR. McCANN: 266. Thank you. I think then we're already to -- Sharon's got something to say.

DR. HERTZ: We don't have the data that Dr. Terman requested, but the sponsor does have the unimputed data.

DR. CONNER: This is Jason Conner. Yes. Dr. Terman, you asked about the non-imputed data for 327 in particular. If we can go to the core slide. This is it, core slide 36. I'm just going to start by showing you the raw. This was the raw data, so you can see how the curves go down. Slide PE-14, here you can see how they go down. This is just the raw data. You can see scores went from, on average, a pain score difference of about 2.5 to 88 divided by 48 is a pain score difference of about 1.8.

Again, we can show you, if you want to, the opioid difference per day here. This is with rescue meds being used and with EXPAREL patients using fewer rescue meds. A-6, this shows then opioid use by day. So you can see the plurality case, and each EXPAREL is in the lowest bin, which isn't true for placebo. And we see some of the biggest outliers tend to be in those placebo

groups. So even with rescue, we saw the significant difference maintained in the 327 study.

DR. McCANN: Any further questions for the FDA?

(No response.)

DR. McCANN: I think we're all set to break for lunch. We're very early. We'll reconvene in this room --

DR. HERTZ: Wait one second. Since we're this early, I also want to open it up if there are any additional questions for the sponsor. This panel is very low on questions; I don't know.

Are there any questions for the applicant?

DR. McCANN: Dr. Terman?

DR. TERMAN: I have another question. Clinically, people will mix epinephrine with local anesthetics to try and notice, before all the dose has gone in, that you've got an intravascular injection. Do you know anything about epinephrine with the liposomes in EXPAREL?

DR. SCRANTON: Yes, we've studied that in admixing with epinephrine, and the epinephrine has

no impact on the release characteristics of the bupivacaine. It's not in our label to recommend co-administration, but we have looked at that, as well as a lot of steroids and numerous amount of medications that don't have any impact on the release characteristic.

DR. McCANN: Dr. Gulur?

DR. GULUR: Thank you, Dr. McCann.

This is to a question that I had asked yesterday. I was wondering if you had any more information on co-administration of other local anesthetics, especially today where we've heard that the peak levels, there's quite a significant scatter. What is the information on co-administration on other infusions, continuous exposure to other medications? There's a lot of information with single-shot bupivacaine, but co-administration is not uncommon, and what is the information for that?

DR. SCRANTON: This was an independent study from us done by Springer, et al., where they actually were doing bilateral total knees. So in

that case, they're doing the cases simultaneously, two different teams, and they're doing a local infiltration of EXPAREL at the full dose, 266 milligrams in each knee, so double our recommended dose. And they were also doing co-administration of 150 milligrams total dose bupivacaine 75 per knee.

They obtained these PK levels throughout the course of that study. At 4 to 8 hours, you can see a peak concentration around 800, and then that dose was decreasing after that time. They didn't notice any neurologic or cardiac complications; so one example of co-administration at the same time in the same area.

Now, we've done re-dosing studies, but our re-dosing studies were done with EXPAREL re-dosing at various time points. We can bring up that particular slide for re-dosing with EXPAREL in the case that someone did have a perhaps failed block, would there be the opportunity to readminister a second dose. We do have that information. This is the re-dosing, multiple doses at time zero, 24, 48.

DR. McCANN: Dr. Xu?

DR. XU: I just have one clarification question. The Y-axis, is that microgram per mL or milligram per mL?

DR. SCRANTON: That would be equivalent to -- we converted -- for us, it would have been equivalent to 800 nanograms per mL, so micrograms.

DR. XU: It should be micrograms.

DR. SCRANTON: Yes, sir.

DR. XU: Okay.

DR. SCRANTON: Thank you.

Just to give as an example, when we're working with the military, the idea was in the future perhaps we could administer in the field of battle, and there would be a concern to do re-dosing. So we did this study in particular to look at a variety of times giving double the dose at time zero, and then try and approximate when the Cmaxes would be 48 or 72 hours, 24 hours later.

What we can demonstrate here is that consistently we saw -- and this is subcutaneously -- a very low Cmax in the subQ

administration. It's just giving us confidence that we can have the expected effect whether or not you're using co-administration or you're doing admixing.

The only other study I have for you where additional free bupivacaine --

DR. GULUR: Before you on, could I as a clarifying on this? What sites?

DR. SCRANTON: This is our healthy volunteers study where we're administering this subcutaneously.

DR. GULUR: In the upper extremity?

DR. SCRANTON: Correct. I will show you the PK study from our two knee studies because it's another way for us to look at that. We have the combination of the two knees studies, parallel, the two PK curves from 323 and 326 comparison and overlap.

As the FDA pointed out, one of the key differences in this particular study was the co-administration of 40 milligrams in the posterior capsule. I'm just giving you another idea. The

FDA showed the PK represented from 323 from only five samples. That's because in the 323, we only measured our initial PK samples up to 72 hours, and indeed, what we determined as Cmax is around 74. We only had 5 patients who actually went beyond that time point.

But when we look at all of the PK samples we have, which is represented here, you can see the Cmax in green from 323 is very close approximating to that, which we observed in 326, pretty consistent. But what you're observing in the very early peak there compared, that is likely the contribution of the free bupivacaine administered in the posterior capsule.

So again, what we would expect, if you're administering free bupivacaine, you're going to get its characteristic peak, and then it's going to be gone and metabolized before you're seeing the Cmax related from the release.

DR. GULUR: I would agree completely, which is why my question is not on single-shot co-administration, but the fact that when you

administer local anesthetics as an infusion, you actually see a peak. It goes up day 1, day 2, day 3. So if that occurs and it meets the peak of EXPAREL, there could potentially be significant toxicity in patients.

DR. SCRANTON: From a continuous nerve block?

DR. GULUR: Confusion of -- not Duramorph. I'm talking about epidurals, other nerve catheters, cases where EXPAREL has not resulted in pain relief, and they choose to put another catheter in and infuse the medication. What guidance is there in co-administration and what the maximum dose should be?

Remember, what people will practice is essentially administering the entire safe dose and that infusion that is known in the literature today. So when you have a concurrent patient who's received EXPAREL in addition, what guidance are we providing them on what is a safe dose, match I guess, between these two?

Some of it, actually, I'm a little bit

concerned because the information that is being sent out is on single administration, one shot, which is leading to a sense of safety amongst people that nothing would happen in you continuously infuse these two.

DR. SCRANTON: And I agree. We wouldn't currently recommend a co-administration of EXPAREL with a continuous nerve block because --

DR. GULUR: You do not recommend?

DR. SCRANTON: A co-administration of continuous peripheral nerve block with EXPAREL. I can have Dr. Gadsden talk about in their clinical practice because I agree, here --

DR. GULUR: Yes, I would love to hear. Thank you.

DR. SCRANTON: Yes, exactly. Thank you.

DR. GADSDEN: Thank you for the question. I hear your concern, and I share your concern. And I think, like Dr. Scranton said, it's probably not the sponsor's intention to advocate for the co-administration of EXPAREL in the setting of an ongoing peripheral, or neuraxial, or intravenous

infusion of local anesthetics. A good example is IV lidocaine, which a lot of centers are doing. I don't simply know the combined plasma level of that lidocaine, which is being administered intravenously or peripheral nerve catheter in the sciatic nerve with ropivacaine, bupivacaine or ropivacaine epidural.

What those plasma levels are, combined on top of the, admittedly, fairly low Cmax with the EXPAREL. So I think this is a good opportunity for us to do those studies, and I'm aware of some things that are in the works in that regard. So my personal preference would be probably to avoid that in my clinical practice if I could.

DR. GULUR: Would you be able to comment on your institutional practice?

DR. GADSDEN: Yes, I can. Our institutional practice is interesting because we have a set of docs that are putting in these drugs in the operating room, and that can be myself as an orthopedic regional anesthesiologist, or we have folks in the cardiac division that are putting in

blocks for cardiac surgical procedures and many thoracotomies.

I think this is the situation that you're alluding to, where you have these blocks, and maybe they're imperfect because of the nature of the block and not necessarily the medication. And then the clinical decision comes up, how do I rescue this patient? So that has led to some tricky decision-making in our institution, and I think we're learning from that and trying to decide what's the best place to start.

DR. GULUR: Would you recommend then, in your clinical opinion, that that not be done until it has been studied and those values are known?

DR. GADSDEN: I can only speak for my own clinical practice and what I would do. I think this is, again, a matter of clinical judgment and an evaluation of the risks and benefits for that particular patient in that particular situation, like we all do in anesthesiology.

So I think personally if I had a patient that was getting an epidural, and I knew that in

advance, I think I wouldn't choose to put EXPAREL in there, or if they had EXPAREL and that failed, the block failed and they happened to use EXPAREL as a local anesthetic, I'd be very careful about doing a subsequent epidural in that patient. And this is going to be something that we as a community all sort of figure out as we go forward.

DR. GULUR: Dr. Gadsden, most institutions have policies around the administration and co-administration of medications, which are evidence based. Would you then suggest that since there is an absence of evidence currently on the safety of co-administration, that most institutions should not adopt a policy that allows the co-administration of these infusions?

DR. GADSDEN: Again, I don't think I'm in a position to dictate policy to other hospitals or departments, but I think it's a good starting point for a conversation and each department to come up with a set of guidelines for their own practice.

DR. SCRANTON: But as a sponsor, I agree. We haven't studied the co-administration with a

continuous nerve block, so our label will read -- or we would suggest it reads that that would not be recommended. Our current label actually does state that for wound infiltration, about not providing additional bupivacaine or IV lidocaine, or other pain --

DR. GULUR: Would you be able to bring up that language if you don't mind?

DR. SCRANTON: Sure. Here's how our current label reads to address that issue. Commonly for bupivacaine, the total dose per the label is a maximum dose of 400 milligrams and 24 for immediate-release bupivacaine. So here our dose is 266 milligram, and not to exceed that dose. I'm not aware of a package insert for IV lidocaine.

DR. GULUR: So a question for you would be, as a practicing clinician who's reading this, if I wanted to co-administer bupivacaine -- because as we just heard, there is independent practice and many may choose to do it for the patient's benefit, co-administration of these medications. The label for bupivacaine reads 400 milligrams per day as a

maximum that should be given.

So when I know that a patient has received 266 milligrams of EXPAREL, am I to subtract that amount for day 1, and what should I be doing for day 2, day 3, or as I've heard, it could be up to day 5?

DR. SCRANTON: What we can best extrapolate from all the PK levels that we observed is that you're seeing a slow release of the milligram exposure, so you're not getting 266 milligrams of systemic exposure on day 1 because it's being released slowly over time. Roughly what you're seeing, 100 milligrams or so on a per-day extrapolation from the dose based on the PK curves as far as what's being absorbed.

That's what we do know from local anesthetics, from bupivacaine. You're getting that high initial peak because that dose, immediately when you apply it into the site, as you well know, rapidly moves away from the nerve and it's getting taken up into the blood stream. In contrast, with our drug, we don't see that, and you're seeing the

more slow peak and release over time. That's where we can best understand about the co-administration.

DR. GULUR: We heard in the FDA's presentation that the scatter for EXPAREL, not just at initial administration but all along, is quite variable in patients. So how am I to make a clinical decision on co-administration?

DR. SCRANTON: We can bring up the bupivacaine scatter, the combined slide. One issue that we're talking about is you're seeing -- we're only talking about bupivacaine being given at a single injection time, and you're seeing all that variability over a single administration. To approximate the variability, I'd have to give repeated injections of bupivacaine.

DR. GULUR: Or do an active control with a catheter study.

DR. SCRANTON: And those have been done at least already. A number of those have been published, but they haven't done PK necessarily but they've looked at efficacy. But this just shows the scatter that you can see from a variety of

nerve blocks, where you can see the confidence limits are also very wide in numerous studies shown with local anesthetics given as a continuous nerve block, or if you had to do a repeat, you would expect that.

Absolutely, these studies are old because no one's really been doing that work with peripheral nerve-block catheters, so I have to go way back in the literature to find these. But they do exist and they show the variability consistent from repeat exposure from bupivacaine, whether from repeat injection, or if you're doing a continuous nerve block. So that's what we're looking at.

DR. GULUR: Another question I have on a separate issue, EXPAREL is something that once you give it to a patient and send them home, they've had a medication that's going to last a lot longer than the expected. If you send them home with a catheter and they had to go back into the hospital or institution, everyone knows what they're getting and the fact that they have something else being administered.

What safety have we put in terms of patient education to ensure the patients who receive EXPAREL -- like with devices, you carry cards or something that tells you that if you go into an emergency situation, people are aware of what medication you've been administered. What safety has been put in place for EXPAREL?

DR. SCRANTON: Actually, for the last six, seven years, that's been a significant part of our training and education, and we provide, for whatever hospital wants, a bracelet for the patient. They go home and tell them they've received EXPAREL. We provide education to both physician and patient on all of those and if the patient has received that drug.

That's also important as I'm traveling around the hospitals to hear that nurses provide that education because it's serving two purposes. One is to educate the patient that they do have a drug that's working 24-7, so you don't necessarily have to get ahead of the pain with opioids. It's reinforced by the anesthesiologist and the surgeon,

so they know when they go home, you may not be having too much pain; don't be too active. Those are all the types of things that are part of the education.

DR. GULUR: I couldn't agree more and that's very important, but I'm actually asking from less the pain relief aspect and more from the safety aspect. If a patient goes into a hospital -- and we all know patient education given at the end of a discharge, et cetera, is poorly retained. So what information -- what weight does a medical caregiver in an urgent medical situation -- how are they alerted that this patient has received EXPAREL in the last 72 hours or 5 days?

DR. SCRANTON: Exactly. Part of that's the training. We have brochures and pamphlets that go home with the patient that shares that. The good news is when they're living 24 hours, 48, 72 hours from a Cmax exposure, at 96 hours, we're at very low levels. So indeed, if they were going to be coming back, they could get re-administered with another local anesthetic per our package insert

because we're at so small levels of circulating bupivacaine.

DR. GULUR: What time period do you feel comfortable about that, co-administration or re-administration? You said within 24 hours, 48?

DR. SCRANTON: For repeat exposure for EXPAREL --

DR. GULUR: Or other local anesthetics, and/or.

DR. SCRANTON: Dr. Roy Winston can address that from his clinical practice and use.

DR. WINSTON: Hi. Roy Winston, Pacira Pharmaceuticals. Actually in the label, right now currently -- and this is not planned on changing -- it does say in the first 96 hours after administration of EXPAREL, no other local anesthetics should be administered during that 96 hours.

I think to your point -- I know Rich mentioned it, but the patients are given bracelets -- I believe they're gray in color -- that they're wearing that discuss the

EXPAREL administration. So to a healthcare provider they can see that just like they would see an allergy bracelet or any identifying bracelet like that. So the important thing is initially you can admix up to 50 percent, and then no other local anesthetics for the 96 hours. And that's already in the label and, again, no plan to change that.

DR. GULUR: So just to confirm, you recommend no other local anesthetic be co-administered --

DR. WINSTON: During the first

DR. GULUR: -- to a patient who has received EXPAREL for 96 hours.

DR. WINSTON: I don't know if we can bring up something that has that language from the label. The label states, "Formulations of bupivacaine other than EXPAREL should not be administered within 96 hours following administration of EXPAREL." And that's been at the label since the beginning.

DR. GULUR: That's very specific to bupivacaine, however, all the data says that local

anesthetic toxicity can be summative like other agents added on. So that specifically says bupivacaine, which is being interpreted as you can give others. Is that correct?

DR. SCRANTON: That's a great point. Thank you. We can clarify with the FDA. That's not the intention, local anesthetics. That's the intention.

DR. GULUR: Thank you.

DR. SCRANTON: Thank you.

DR. McCANN: Dr. Litman?

DR. LITMAN: Thank you. Dr. Scranton, before our break, you had put up a slide that I just didn't get enough time to look at. You had showed all the other clinical studies that had been done that were not presented here today, that were I assumed published or that you just knew about.

DR. SCRANTON: These were all studies that were published. Yes, correct.

DR. LITMAN: Forgive my ignorance. This is a question out of naiveté, and Dr. Hertz, if you can help answer, too. How do the results or the

patients that are included in these studies figure into FDA approval?

DR. HERTZ: That was not submitted with the application, so not at all, other than if we become aware independently of safety concerns, then we can pursue them. But we haven't reviewed any of those studies.

DR. LITMAN: Okay. Thank you. I was wondering about that. Thanks.

DR. SCRANTON: Thank you.

DR. McCANN: Dr. Zacharoff?

DR. ZACHAROFF: Kevin Zacharoff. I was wondering if you could bring back up the slide where the fourth bullet point, or the bottom bullet point, or one of the bullet points talked about the use of lidocaine or other local anesthetics in patients who had EXPAREL. You just had it up a couple of minutes ago.

DR. SCRANTON: Bullet point for our label. Our current package insert that speaks about this.

DR. ZACHAROFF: "Non-bupivacaine based local anesthetics, including lidocaine, may cause

immediate release of bupivacaine from EXPAREL if administered together locally." So just so I can be clear, are we saying that a patient who's had EXPAREL for 96 hours should not be exposed to a non-bupivacaine local anesthetic, period?

DR. SCRANTON: Two things. The co-administration is specific when you admix the two together and put them in the same area. Any lipophilic anesthetic like lidocaine or ropivacaine will compete for the binding site for bupivacaine and displace that. So you will basically have a long-acting/short-acting lidocaine, and then you will have bupivacaine. It would have to be on equal molar.

We started that out to 20 minutes and being pretty conservative that if you separate in time from that, it has no impact on the release of our drug. So if you're going to give lidocaine, wait 20 minutes, then give EXPAREL, that wouldn't have any impact. Also, if you're giving lidocaine at some other site, you're putting in an IV and need a little lidocaine, that wouldn't have any impact on

our drug whatsoever.

DR. ZACHAROFF: So we're only talking about local co-administration.

DR. SCRANTON: Correct.

DR. ZACHAROFF: Getting back to yesterday -- I believe it was yesterday -- you talked about -- or maybe it was this morning -- the ability to precipitate early release of the bupivacaine from the liposomes. And I was wondering if you could just expand on what situations could provoke premature release of bupivacaine from the liposomes.

DR. SCRANTON: Really, the only one -- if you'd rather soap, your betadine, that type of -- right in close proximity will break down the liposomes. But otherwise, all the other co-administration with steroids, with epinephrine, other drugs commonly used when we were studying this anticipation in using it in total knees -- and surgeons like to use a lot of co-administration. We did ketorolac, opioid, tranexamic acid, clonidine, commonly used surgical materials. There

was no impact on the release characteristics of our DepoFoam.

DR. ZACHAROFF: So what about any patients develop postoperative infections or anything like that, pH changes?

DR. SCRANTON: Not that would be compatible with that patient. You'd have to get extremes of pH, that they were really toxic before there would be any likelihood that that would impact the tissue level release characteristics of EXPAREL.

DR. ZACHAROFF: Thank you.

DR. McCANN: Dr. Gulur?

DR. GULUR: I just wanted to clarify again. I'm sorry. I may have misunderstood. The language you had read out regarding the 96 hours, is that only admixture and local administration, co-administration? Because we are dealing with two issues here. One is mix and inject into the same local site, which has issues about release of the bupivacaine from the formulation versus the other safety issue, which is the PK of systemic absorption of EXPAREL and then having additional

local anesthetics administered on top and what's the safe dose range for something like that.

DR. SCRANTON: Go ahead.

DR. WINSTON: Right. To take those one at a time, I think for the admixing, that's up to 50 percent of the dose. So with the 266-milligram initial dose, you can do half again with plain bupivacaine. And then after that's administered, we recommend no other local anesthetics for 96 hours.

DR. GULUR: At the same site, no other local anesthetics.

DR. WINSTON: For the same patient; really, at any site at that point. Now again, what Dr. Scranton said, if someone's using a half a cc to start an A-line or an IV, that's a non-factor. But at that point, I wouldn't want someone to go in with a full dose of ropivacaine and repeat a block, for instance, on that patient.

DR. GULUR: Repeat a block at the same site --

DR. WINSTON: At the same site.

DR. GULUR: -- put the block somewhere else?

DR. WINSTON: Same site. So typically, you do an interscalene block, and the patient wakes up afterwards, and it doesn't have a complete block or has a failure. I think a couple of hours have gone by. Most of us who are using ropivacaine or bupivacaine plain, we would probably repeat that block. With EXPAREL, we recommend once you do it, not to repeat it with anything other than EXPAREL at that time, at that site.

DR. GULUR: To follow that thought, you can, though, on the other hands use an equal amount of local anesthetic at the other sites. You could do a femoral block. You just did a shoulder, and the patient also has a lower extremity. I could do another block in the lower extremity.

DR. WINSTON: But again, your starting dose, you wouldn't want to exceed the recommended 50 percent totally anywhere in the body at that point. And I think really, from a safety concern, we know that the PK cumulatively from the EXPAREL and from that added 50 percent of bupivacaine won't

stack on top to hit a level. Then if you start blocking elsewhere in the body during that time, that's something we don't recommend.

DR. GULUR: You do not. And is that clear in your label? Does that indicate that you should not?

DR. SCRANTON: So we have not had that for the nerve-block label, and that's where we can talk with the agency about adding that additional clarity about not to exceed or repeat dosing with other drugs other than EXPAREL, similar to how we've had the language for our wound infiltration, which we also recommend not to do repeat to bupivacaine.

DR. GULUR: Was that in that slide you showed us, this language?

DR. SCRANTON: That's from our wound infiltration. We haven't, with nerve block, perhaps to your point, talked about adding additional clarification with regards to repeat nerve block with other things other than EXPAREL.

DR. GULUR: And without confounding the

issue with nerve blocks, even with the infiltration, which is current indication, can I run an IV lidocaine infusion in this patient, or is your label basically saying do not --

DR. SCRANTON: Do not.

DR. GULUR: -- do not.

DR. SCRANTON: Correct.

DR. GULUR: Okay. Thank you very much.

DR. McCANN: Dr. Galinkin?

DR. GALINKIN: This question is actually for Dr. Hertz. I have a question. Maybe this is my ignorance. I haven't been to many local anesthetic meeting.

To get a labeled indication for this drug and get a change in labeling, what needs to be demonstrated? Just safety, efficacy, or what? If it's just safe, is that enough or what actually needs to be shown?

DR. HERTZ: Efficacy and safety.

DR. GALINKIN: Efficacy versus placebo, versus an active control?

DR. HERTZ: You would think that's a simple

answer. It has to show efficacy in a reasonable clinical study. So efficacy against the placebo is an option; hence, the two placebo-controlled studies in the current label. So to get just that efficacy in a nerve block would just require any comparator. To get a comparative claim to imply something different than other bupivacaine would require direct comparison.

DR. McCANN: Are there any more questions?

(No response.)

DR. McCANN: Then I think we can break for lunch. We'll reconvene in this room at 12:30. Please take any personal belongings you may want with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any member of the audience. Thank you.

(Whereupon, at 11:09 a.m., a lunch recess was taken.)

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

(12:30 p.m.)

Open Public Hearing

DR. McCANN: Welcome back. We're about to start the open public hearing portion of today's meeting.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee on any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment for your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement

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

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

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization that you are representing for the record.

DR. HAVARD: Thanks to the committee for

allowing me to be here to speak today. My name is Dr. Drew Havard, and I'm a practicing oral and maxillofacial surgeon. I'm speaking on behalf of Dr. Pedro Franco in our practice in Irving, Texas called DFW Maxillofacial Surgery, P.C. My travel expenses to present at this open public hearing are supported by Pacira Pharmaceuticals.

For the last four years, our oral and maxillofacial surgery practice has implemented an opioid-free environment for the management of postoperative pain after major and minor oral and maxillofacial surgery procedures following a specific multimodal pain regimen protocol with EXPAREL.

The goal was to decrease the amount of opioids used for postoperative pain during the hospital stay and the amount of opioids prescribed after the patient was discharged home. The initial results were very positive, including decreased or even non-use of opioid patient-controlled analgesia pumps as well as oral pain medication during the hospital stay.

The same findings were observed during the following days after the patients were discharged. We then further decreased the amount of opioid tablets prescribed with no refills. We also stopped using PCA pumps and started using NSAIDs intravenously and orally during the hospitalization and after discharge.

The outcomes were very satisfactory and the patient comfort level for pain was high during the initial 72 to 90 hours. Even the nursing staff at the hospital commented on the lower amount of pain reported by our patients and the fewer side effects like nausea, vomiting, constipation, euphoria, respiratory depression, and changes in heart rate and blood pressure. The patients were recovering faster and being able to go back to their normal tasks earlier than before. Also, caregivers reported less time needed with the patient during the recovery period due to the fast recovery.

At this point, our protocol includes a multimodal pain management, including interoperative EXPAREL locally injected on the

surrounding areas of the surgical site. The patient is discharged home with a combination of NSAIDs and acetaminophen for a period of 5 to 7 days. Postoperative visits related to negative side effects have been decreased significantly.

Opioid prescriptions are not routinely prescribed to our patients. We support the usage of EXPAREL in the field of oral and maxillofacial surgery for nerve blocks after the proper training by the specialized clinician. EXPAREL for nerve blocks will keep the patient in longer periods of comfort with lower pain levels after major jaw corrective surgery, temporomandibular joint surgery, facial reconstructive and trauma surgery, as well as regular oral surgery. Thank you.

DR. McCANN: Would speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. BAO: Hello. My name is Xiadong Bao. I'm a physician anesthesiologist at the Mass General Hospital, and I'm the study PI at the

[indiscernible] site for the EXPAREL knee and shoulder studies. I'm here today to describe my experience with the EXPAREL trial and tell you what I've observed for the studies.

When I first initiated the study, I was not totally convinced. I was suspicious. I was concerned. By nature, I'm a disbeliever. I just don't believe what other people say. That's mainly because my PhD training is that many times you just cannot replicate other people's data until you do it yourself.

We followed the study protocol very strictly because I really wanted to see if it's what they say it is. I was there to observe my patients day and night, and I did the mini main [indiscernible] block first-handed and did the main physical exam myself, even at midnight to 2:00 in the morning. The reason I found I was actually pleasantly surprised or not surprised is that many of my study patients, they do have prolonged nerve block, and some of them have the sensory deficit up to 5.7 days, which is not surprising to some, but it

was a pleasant surprise to me.

The other phenomena I want to emphasize was what I observed about the smooth recovery of my patients after the shoulder and the knee surgeries. In orthopedic literature, there's a well described phenomenon called the rebounding pain, which means when block is gone, your pain is back, and the pain is severe, and the patient frequently requires escalating dose of narcotics. In fact, in many studies, we note for single-shot interscalene block, it lasts about 6 to 8 days, and the patients will have more pain when block is gone. At a 24-hour time point, they actually require more narcotics compared to a patient without interscalene block. So patients will often describe that my pain continues day and night. When block is gone, it's really, really bad.

In our study of patients, their recovery process was much smoother. They don't appear to have a turning point during their recovery and there is no traditional rebounding phenomenon that we observed. We actually saw our patients, when

they get discharged, they tell me they don't even require the pain medication to go home. So in my opinion, this is a very smooth transition and it improves the patient's recovery to help them to regain their functional status. Thank you.

DR. McCANN: Will speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. MOSER: My name is Jim Moser, and I'm from East Kingston, New Hampshire. I flew here this morning at my own expense. I have no affiliation with Pacira, and I'll be at work tonight. I'm a scrub tech in a local hospital. My motivation to come here is both professional and personal. My wife Jean and I lost our son Adam to a fentanyl overdose September 2015; bright, multilingual, kind and engaging, an actuarial science graduate from Temple University.

Adam had what he called a prescription pain pill hobby. He called it a hobby. We didn't know about this hobby until the state trooper knocked on

our door and told us he was dead. I mentioned he died from fentanyl, and you're well aware that opioid use has a tolerance and escalation factor and typifies too many that die from fentanyl, an involvement that begins much earlier. Behavior is complicated by the presence of excess prescription opioids. As parents, we never appreciated the potential for addiction, euphoria, or misuse, or the need to secure the product when it's in our home, and safely dispose of it afterwards. Our kitchen cabinet was our medicine cabinet. Shame on us.

From all of that came an initiative called Zero Left, Zero Left doesn't say don't prescribe; it says when you do. The initiative educates about prescription opioids when they're in your home, it's practiced at five New Hampshire hospitals, and includes physician education programs.

During one of these programs, Dr. Gonzales of Manchester spoke about the use of EXPAREL as a regional block in his practice as game-changing, and I came here today to tell you that. To quote

Dr. Gonzalez, "We see decreased pain in opioid use, improved patient satisfaction, an earlier return in my EXPAREL patients. I believe that when used as an anesthetic and a peripheral nerve block for knee replacement surgery, EXPAREL will prove more effective, and it's currently approved for on-label use. I also believe the safety profile will be unchanged with that application.

"As orthopedic surgeons, we use a variety of tools to provide comfort to our surgical patients. We've come to recognize the high cost of liberal opioid use amongst our patients, families, and society in general."

Dr. Gonzales sends his patients home with 50 short-acting opioids. When I went home for my own knee replacement, I had an initial dose of 150, three times as many. So I'm here representing the people whose lives have been changed by excess prescribing. And for all of us, we need opioid alternatives, and we need them as soon as possible. We can still treat pain, but with better and different products, and this use of EXPAREL is one

of those examples. Please consider this. Thank you.

DR. McCANN: Will speaker number 4 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. BONO: Good afternoon. My name is Mary Bono. It's a privilege to appear before you today in my capacity as a patient and advocate and a policy maker when I served in the U.S. House of Representatives from 1998 to 2013. I do not have any direct financial relationships with the applicant company. My employee [sic] Faegre, Baker, Daniels works with a wide array of life sciences clients that does not represent, nor do I have any relationship with Pacira, but they did provide auto transportation today.

The bulk of my interest in being here today comes from the fact that my son is in long-term recovery from an addiction that began with an opioid prescription drug like so many others as we've just heard. There is a significant

relationship between the use of opioids to treat both acute and chronic pain and the epidemic of abuse, addiction, and overdose washing over our entire country.

When I was in Congress, I started the Prescription Drug Abuse Caucus with Congressman Hal Rogers to rally our colleagues on Capitol Hill, and as I was a chairman of an oversight committee, I held a series of the earliest congressional hearings to examine the scope of the problem and the role the federal government had in mounting a comprehensive response. Congressman Rogers went on to launch the RX Abuse Summit, which is unquestionably the most important, convening each year to focus the nation on how the epidemic is evolving and the best practices for confronting it.

Since leaving Capitol Hill, my work has continued to evolve around preventing opioid abuse and strengthening addiction treatment. Together with the Trust for America's Health and the Community Anti-Drug Coalitions of America, we created the Collaborative for Effective

Prescription Opioid Policies also known as CEPOP. And it's there in partnership with nearly 80 national organizations that I have learned so much about the need to invest in and develop innovative therapies that can help people manage pain in a way that reduces the risk of addiction, adverse events, and other harms. I want to applaud the FDA under Commissioner Gottlieb's leadership for making this a priority as well.

Turning to the specific application for label expansion for EXPAREL, while I'm certainly not an expert in evaluating the data, I can say that this product, both for its current indication and the proposed expansion, is entirely consistent with what we need to be doing. Non-opioid medications and other alternatives must be discovered, developed, brought to market, and made available to clinicians and patients through their health plans.

Coincidentally, I have first-hand experience with EXPAREL. Last year I had soft-tissue surgery, and the surgeon used EXPAREL during that procedure.

I had good pain control in the clinic and was able to limit my exposure to opioids for only a brief day or two. This is a big part of the reason that I'm here today, the patient experience.

Thank you for the opportunity to speak today and good luck with your decision.

DR. McCANN: Would speaker number 5 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. TIROTTA: Good afternoon. My name is Dr. Christopher Tirotta. I'm the chief of anesthesia at Nicklaus Children's Hospital in Miami. I want to thank you all for having me. Pacira did pay for my travel expenses here, but I have no other financial relationships with the company.

My first exposure to EXPAREL actually did not come as a practitioner; it came as a patient. In the last two years, I've had two surgical procedures, a right hip arthroplasty and a lumbar decompression for spinal stenosis, and I received

EXPAREL at both times. During the first procedure, I did not want to micromanage what the anesthesiologist was going to do, so I got fentanyl interopratively. I got morphine postoperatively. I was planning to go home. I was extremely nauseous and was unable to do that.

During the second procedure, I did tell the anesthesiologist I wanted no narcotics. I had EXPAREL. I had no pain for three days at all. It was a remarkable experience, and it set me on a mission to get this drug approved by our PNT committee. This was kind of a heavy lift because there's a dearth of literature on the use of EXPAREL in the pediatric population both for efficacy and safety.

After many meetings and a lot of convincing, they did allow the drug to be used, and we've been using it in our institution for the past year on probably several dozen patients with excellent results and no local anesthetic toxicity. Please bear in mind that we use bupivacaine in all age groups, including newborns. I'm a very big

proponent of multimodal anesthesia, multimodal analgesia, and a very big proponent of not using opioids for postoperative analgesia. I think they have severe side effects at times. I experienced that myself. So we try to provide postoperative analgesia without opioids.

The pediatric population is the most vulnerable population that we treat. We provide general anesthesia for many surgical procedures that are normally done with local in adults: cardiac CAST, invasive radiology procedures, biopsies, et cetera. If we think it's inhumane not to adequately treat postoperative pain in adults, it's doubly inhumane not to treat it adequately in children. So I strongly urge the expansion of the use of this drug. It's a wonderful advance in medicine. Thank you.

DR. McCANN: Will speaker number 6 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SESSLER: Good afternoon. I'm Dan

Sessler. I'm [inaudible - audio gap] of the Department of Outcomes Research at the Cleveland Clinic. My visit here is supported by Pacira, but I'm appearing in a personal capacity. By way of background, I'm board certified in both pediatrics and anesthesia. I've published more than 700 full papers, which have been cited more than 30,000 times.

When I was a resident, it was still common for infants to be given nothing except a muscle relaxant, the theory being that what the infants didn't remember wouldn't hurt them. Fortunately, there is now a broad understanding that infants and children suffer pain just the way adults do, deserve comparable analgesia, including postoperative analgesia.

Perhaps because they are easy to provide, opioids remain the most common postoperative analgesic. But they are almost disastrously bad. Hyperalgesia intolerance developed quickly. Opioid-induced respiratory deaths remain common, even in hospitals, and staggering fraction of

opioid-naive patients who come for surgery are still on opioids six months later. Some of them never stop.

Local anesthesia, field blocks, and nerve blocks are distinctly preferable to opioids. The difficulty is that local anesthetic blocks provide great analgesia for as long as the anesthetic lasts, but that's usually about 12 hours, which means that the block wears off in the middle of the first postoperative night when patients have little access to alternative analgesics and little access to healthcare providers.

Encapsulated bupivacaine is a distinct advantage because it lasts for days. This gets patients through the very acute, several days of sharp surgical pain. Thereafter, it's almost always possible to transition patients directly into a non-opioid alternative. Because of its obvious duration benefit, encapsulated bupivacaine is frequently used in pediatric patients off label. For example, at the Cleveland Clinic, we identified 500 pediatric patients who had encapsulated

bupivacaine. After careful chart review, we did not identify even a single toxicity attributed by our adjudicators to local anesthetic.

We matched these patients 2 to 1 with similar patients given bupivacaine. There was no difference whatsoever in the number of complications or in the range of complications.

DR. McCANN: Dr. Sessler, could I have you wrap up your last comments there?

DR. SESSLER: I have one sentence. Encapsulated bupivacaine thus appears to be safe even in pediatric patients and is clearly preferable to opioids. Thank you.

DR. McCANN: Would speaker number 7 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. MOORE: Andy Moore. I am a recently retired plastic surgeon from Lexington, Kentucky. My travel expenses have been paid by Pacira. As a practicing surgeon for 35 years, I found EXPAREL helpful in transitioning patients from an

in-hospital setting to an outpatient, a great savings, as well as an effective pain relief.

In 2005, I founded Surgery on Sunday, not for profit that provides free outpatient surgical procedures to patients who have no insurance or who are underinsured. We have taken care of approximately 6,000 patients.

Unfortunately, Kentucky is in the epi center of the opioid problem of this country. Through a generous donation of EXPAREL, we have developed protocols using EXPAREL. We have found it helpful in expediting the patients' discharge from outpatient surgery as they do not require any narcotics in the postoperative recovery room. Patients also are either discharged on no pain medications or much less. For example, we do hernia surgeries, and this is one of our most common procedures with EXPAREL, and we discharge these patients on Tylenol. This leads me to believe that EXPAREL is part of the opioid crisis solution.

On a personal note, in April of last year, I

had a rotator cuff procedure and at that time had a pain pump employed. I required no opioids postoperatively, but I found that the pump was annoying and short-lived. I wonder if EXPAREL as a block would have been more effective. Thank you for the opportunity to allow me to testify.

DR. McCANN: Would speaker number 8 step up to the podium and introduce yourself? Please state your name and any organizations you are representing for the record.

MR. MENDELL: Hi. Good afternoon, everyone, members of the Anesthetic and Analgesic Drugs Product Advisory Committee. My name is Gary Mendell, and I'm the founder and CEO of Shatterproof, a national nonprofit dedicated to reducing the devastation the disease of addiction causes family. I'm here to speak in full support of Pacira Pharmaceuticals' EXPAREL.

First of all, I would like to say that I became aware of EXPAREL when we partnered together with Pacira in educating the public about this product at our 5Ks around the country. Pacira, to

note, is one of our sponsors at these 5Ks. I would also like to state that Pacira Pharmaceuticals did not pay for my travel here today.

Related to my qualifications, I'm a father who has had the anguish of having to have buried his first born son who was addicted to opioids. My son Brian was 25 years old when he died. In the months following Brian's death, I left my 25-year career in business and dedicated the rest of my life to sparing other families from this unspeakable tragedy that my family has endured.

I firmly believe that the use of this nerve block can minimize exposure to opioids, therefore it will significantly prevent potential risk of addiction to patients having surgery. If physicians reduced the number of opioid prescriptions written each year by just 10 percent, it would result in 300,000 fewer patients becoming persistent opiate users following their surgery; 300,000 per year, almost a billion dollars, $830 million a year in lower drug costs.

As you know, deaths from drug overdose have

been rising steadily over the past two decades and have become the leading cause of injury death in the United States. EXPAREL provides significant long-lasting pain control while reducing this opioid use. This is a win-win for patients and our medical professionals.

In closing, I would just like to say that since my son passed away six years ago, I wake up every morning knowing what I cannot change. My son will not be coming home. But I also wake up every morning knowing what we can change. Today this committee can take a step forward and create a change by providing a viable alternative to manage pain and significantly reduce opioid use for patients having surgery. Thank you so much for your time and considering this important product.

DR. McCANN: Will speaker number 9 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. LITZ: Hello. My name is Stacy Litz from Middletown, Ohio, and my travel and expenses

were paid by Pacira for me to be here today. Standing here today giving my testimony is one of the easiest tasks I've ever been asked to do because overcoming the addiction to opiates was the hardest. I couldn't grasp the fact that a pill smaller than the tip of my pinkie was able to consume me and cause me to lose so much in such a short amount of time. I trusted my doctors to fix me unknowing that the medications they were giving me was leading me into my addiction.

I had back surgery in July of 2007 after experiencing extreme pain in my neck, shoulders, and arms due to an unknown herniated disc that I had received from an auto accident just a year prior. This pain came on during my third pregnancy, and it wasn't until I was in my second trimester that an MRI had discovered an issue in my upper spine.

I was given a mild pain reliever in my third trimester and referred to a neurosurgeon after delivering. After being advised that I could have permanent paralysis from the neck down without

surgery, the disc was removed and a bone infusion was put in place. I was then given opiates and referred to pain management. That set the ball rolling. The pain I had endured had brought on a fear of not being able to hold my newborn son. All that I knew about the meds that I was given was not to operate heavy machinery and that there may be side effects such as nausea, constipation, or diarrhea. I found myself wanting, needing, and having to have more and more of the narcotics in order to get through my day. I had no true concept of what habit forming was because in addiction I was consumed.

Since my recovery from addiction, I have dedicated my life to helping others to overcome their disease of addiction by becoming a state certified peer support specialist working at several different recovery facilities. Throughout this journey of the past nine and a half years that I have been drug free, I have heard several similar stories such as my own, estimating that nearly 75 to 80 percent became addicted after having a

surgical procedure and given opiates to control their pain. If only an alternative non-opiate medication would have been administered, how many lives would have been saved?

I truly believe that with the opiate epidemic that we are currently battling, that an alternative is a huge step in the right direction. We can achieve that step with EXPAREL. Thank you.

DR. McCANN: Will speaker number 10 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SHAPIRO: Thank you for the opportunity to speak today. I am Dr. Danielle Shapiro. I'm a physician and senior fellow at the National Center for Health Research. Our center scrutinizes scientific and medical data and provides objective health information to patients, providers, and policy makers. These are the views of the National Center for Health Research and not necessarily my own personal views. We do not accept funding from the pharmaceutical industry, and therefore I have

no conflicts of interest.

It is imperative to address the root causes of pain and opportunities to safely prevent and treat it. Helping patients avoid opioids in the post-op period may prevent pain conversion from acute to chronic pain and also avoid opioid addiction. In order to achieve these two goals, opioid-sparing pain meds must be safe and effective in the post-op period.

Medications like EXPAREL may be the answer, but based on the available data, there is insufficient evidence to recommend supplemental approval at this time. The sponsor has not adequately demonstrated efficacy supporting the proposed supplemental indication. Half of the clinical trials showed no significant benefit.

Neither trial, C-322 or C-326, demonstrate adequate evidence that this drug works for individual nerve blocks. The other trials do suggest potential efficacy for brachial plexus or femoral blocks, but given the mixed results for the new femoral block studies, it is possible that

demonstrated efficacy in one instance was due to chance.

Additional studies which include active comparator arms are needed to provide conclusive evidence. The sponsor should be required to replicate positive results before the drug is approved for this indication. The post hoc analysis should be taken as exploratory rather than a true demonstration of efficacy.

In addition to our concerns about safety, we are concerned about the OSE findings, which showed an association between EXPAREL and a local anesthetic systemic toxicity. Furthermore, knee replacement patients were more likely to fall in the C-326 treatment arm.

Given early mobility is a key to recovery for joint replacement surgery and inpatient fall is counter-productive at best, discouraging patients from walking after surgery. We agree with the sponsor that such patients should not be given EXPAREL, and if EXPAREL is eventually approved and more conclusive data are provided, this warning

should be clearly marked as a contraindication on the label.

Finally, because the PK of this drug varies so widely based on selective block site and technique and the PK data are unavailable for other sites, there is insufficient data to establish dosages for any chosen nerve block that best achieves a balance of therapeutic efficacy and safety.

In conclusion, we need post-surgical treatments that spare patients from opioid use. At this time, however, data is insufficient to recommend approval. The evidence must be replicate and well designed studies that are controlled with an active comparator arm. Currently the data are not adequate to support the change in the product indication or label. Thank you for the opportunity to share our perspective.

DR. McCANN: Will speaker number 11 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. STEELE: Hello. My name is Bob Steele, and I'm from Massachusetts and Florida. I was a patient in Dr. Bao's study at Mass General Hospital. I would like to thank the FDA for the opportunity to give my testimony and to Pacira for paying the expenses for me to be here.

I was contacted in the fall of 2016 to see if I would be willing to participate in a study of a medication that would be helpful in mitigating the current opioid crisis. As an aside, I attended the funeral of a former colleague's son in the summer of 2016 who died as a result of opioid overdose. This was the second of three sons to die this way, and her husband, who was a police officer, died of a heart attack between the death of her boys. She and her remaining son gave powerful and impactful eulogies that moved me to become a study participant.

I underwent a left shoulder arthroplasty December 2016 at Mass General Hospital in Boston. There were three of us in this double-blind study undergoing the same surgery. The study consisted

of sensory stimulation to my shoulder, arm, and hand every 6 hours trying to identify four different objects: a Q-tip, pinprick, cotton swab, and a cold metal object. Each day I made progress in the number of objects identified beginning with the feeling in the hand, lower arm, upper arm, and finally the shoulder area, which was by the third or fourth day of the study.

I have had two other major surgeries in my life, an intestinal operation as a result of an outpouching of the diverticulum and for convenience, the removal of the appendix at the same time. The second was an uneventful gall bladder operation.

I remember receiving shots of morphine and a drip for pain for several days after the intestinal operation. I feel I was in less pain after the shoulder surgery and didn't need pain medication until some time during the third day. I did request sleep medication each night. I had no side effects from the drug, was able to eat from the menu, shower with assistance, walk in the hospital

with supervision, and begin occupational therapy on the second day.

I am now having problems with my other shoulder. When I went for my nine-month follow-up after the surgery, the doctor took an x-ray of the other shoulder. Sure enough the osteoarthritis has begun to set in, and I may need surgery at some point in the future. After having such a positive experience with EXPAREL, I will ask the anesthesiologist to administer it if it is approved. Thank you.

DR. McCANN: Would speaker number 12 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. MONT: My name is Michael Mont. I was the chairman of Cleveland Clinic until a few months ago. I will be moving to New York City in April. First of all, I want to thank the FDA for the opportunity to present here. I am a consultant for Pacira, but since I'm local right now, I'm here out of my own cognizance and got no reimbursement for

travel.

I want to say that there are so many dramatic numbers about the opioid crisis. We hear these statements like one person dying of an opioid overdose every 19 seconds in the United States, and a lot of that is attributed to post-surgical causes. I actually really do believe these numbers. I do knee replacements and hip replacements. Knee replacements, those are some of the most common procedures that we perform in this country, and they're also some of the most painful procedures.

I was the PI of the PILLAR study that I think you're aware of to some extent, and we had dramatic response to liposomal bupivacaine where there was much decreased pain in the EXPAREL group versus bupivacaine alone. But what was really dramatic is that 10 percent of the EXPAREL group did not use any opioids after their knee replacement in that study. The control group had zero percent. And in fact, at the Cleveland Clinic, when I'm using EXPAREL and a lot of my

colleagues, the fellow joint replacements which we are using, that number is close to 20 percent, which is tremendously dramatic.

We used to give patients 6 weeks of opioids when they went home after surgery. Since I was there -- I was there for about a year and a half to two years -- that went down to 4 weeks, and now it's 1 to 2 weeks. And we're not getting any unintended consequences. We're not getting patients that are coming back, getting readmitted three days later. We're not getting extra visits to the emergency room.

It has been part of an effort by the Cleveland Clinic. I think their goals are to try to make it an opioid-free institution, so this is just one of the many things that we're utilizing. I will be using it at the institutions that I'm going to in New York City, and I hope it's espoused by the other institutions throughout the country and the world.

I really applaud Pacira's efforts to try to advance this field and put out other modalities

that may be part of the armamentarium to reduce the opioid epidemic. Thank you for your attention.

DR. McCANN: Would speaker number 13 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. WOODS: Good afternoon. My name is Beverly Woods, and I'm honored to be here. My expenses are being reimbursed by the Pacira Corporation. A year ago, I had total knee replacement and took part in a nerve-block trial for the Pacira Corporation. My adventure began with a severe limp, and I soon found out that the cartilage in my left knee had totally disappeared. I had cortisone shots, but the limp continued.

A good friend of mine who had knee replacement urged me to go see a surgeon. On my second appointment at Mass General in Boston, the doctor asked me if I wanted to take part in a trial for a long-lasting nerve block. I agreed. No pain; that was for me. No doubt, I was one of the oldest, 80 years old. I was in good health, no

prescription drugs except an occasional one for an irritable bowel.

On the morning of the operation, I was given one shot of the nerve block. Amazing, no numbness. I had requested a spinal instead of general anesthesia. Later, I woke up in my room, no pain. The trial doctor and nurses visited that night, and the next morning I was moved to a special unit headed by Dr. Bao. I had walked to the lavatory that morning and had no pain.

In five days, I wasn't aware that the block had ended except when the nurses tested my feeling using the feather and the metal object. I could feel both. After five days, I left Mass General for rehab. I was so impressed with this block that even though I knew it wouldn't make me rich, I bought 100 shares of Pacira stock when I returned home.

I had a new lease on life achieved without pain. I'm so grateful that I was chosen for this trial. Thank you all, and thank you to Dr. Bao.

DR. McCANN: Will speaker number 14 step up

to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. KENT: Good afternoon. My name is Michael Kent, and I'm currently an anesthesiologist and acute pain medicine physician at Duke University Medical Center. My views are my own and do not represent my institution. The sponsor has supported my travel to attend today.

I'd like to voice support for the indication of EXPAREL in the setting of peripheral nerve blockade. I've used EXPAREL in a variety of settings: adductor canal blocks for knee arthroplasty, fascia iliaca blockade for hip arthroscopy, and a variety of other locations to treat post-traumatic musculoskeletal pain. Additionally, I lead a longitudinal DoD patient-centered biopsychosocial outcomes registry, notably supported by the sponsor, focused on extending the role of acute pain medicine tools only one of which is EXPAREL, not only within the first few days post-insult, but in the subacute

period until functional recovery is achieved.

I commend the FDA reviewers on their keen analysis of the studies that have occurred since the last hearing, and admittedly I agree with many of your assertions. However, I submit that the documented efficacy in study 1601 with median and ulnar nerves and 1602 with tibial and deep peroneal nerves answer the question for myself and many other clinicians in terms of EXPAREL being a reasonable tool within the practice of acute pain medicine.

If TAP blockade is allowed on the label, then I submit that there already is a partial indication peripheral nerve blockade as TAP block is merely a glorified intercostal block as it pertains to the abdomen. If efficacy of perineural blockade solely rests upon the size or complexity of the nerves to be blocked, or comparison to techniques is required that only exist in certain specific systems, it has to be recognized that these nociceptive models also become more complex such as a knee arthroplasty or thoracic surgery,

where in the realm of pain research that unfortunately still focuses on pain intensity scores and opioid use, modest benefits might actually be impressive.

Regional anesthesia is only a tool within acute pain medicine, and national data suggests that it still consistently is used primarily due to resources in a variety of surgical practices. With federal and state mandates to turn off the opioid spigot directly post-op in a binary black and white manner, we in acute pain medicine need more tools. We have a variety of pharmacologic agents, but often they need tailoring and hold their own risk for certain patients.

Do I believe EXPAREL will dominate the field of regional anesthesia? Absolutely not. However, I do believe that there is enough evidence that is reasonable to suggest that acute pain medicine physicians like myself can explore delivering this drug to the right patient, at the right time, and at the right nerve. Thank you for your time.

DR. McCANN: Will speaker number 15 step up

to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

(No response.)

DR. McCANN: Would speaker number 16 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. BORGEN: Good afternoon. My name is Patrick Borgen. I'm the chairman of surgery at Maimonides Medical Center in Brooklyn, New York. Prior to that, I was the chief breast cancer surgeon at Memorial Sloan Kettering for 17 years. Pacira Pharmaceuticals has agreed to reimburse me for my train ticket here and hopefully back home to Brooklyn this afternoon. Thank you for the privilege of sharing our experience.

I'm strongly in favor of expanding the indications for the use of liposomal bupivacaine, which has profoundly changed our practice in Brooklyn. With an annual usage in more than 1500 patients, I can personally attest to its safety and

its efficacy. I have two brief messages.

I would like to begin by sharing an in-house study in patients undergoing breast cancer surgery that we just unblinded one week ago. The study was designed to simply compare outcomes based on current surgical practice. The two groups were very different. One group used interoperative bupivacaine, and the patients were discharged with an average of 55 morphine milligram equivalents of opioids. The second group participated in an enhanced recovery after surgery protocol that included acetaminophen, liposomal bupivacaine field infiltration, and Toradol.

None of these patients, zero, received postoperative opioids. In the first 150 cases, the non-opioid group had significantly lower pain scores and significantly higher patient satisfaction scores. Secondly, in my specialty of oncology, there's a growing body of evidence that suggests that systemic opioids may negatively impact cancer outcomes.

The proposed mechanisms for these outcomes

are beyond the scope of this presentation, but I would argue, strongly, that the debate itself is enough, while larger studies are underway, to justify striving to replace opioids with better regional anesthetics such as EXPAREL. Finally, at the beginning and end of our debate are our patients. Patients who deserve to be as pain free as possible without the worry of addiction or worsening of their prognosis.

In conclusion, many people are surprised to learn that nowhere in the Hippocratic oath does it actually say primum non nocere, first do no harm. Hippocrates never wrote that. That was added in the 17th century. What the Hippocratic oath does say, however, is, "I as a physician pledge to do my best through my studies and learning to utterly reject harm and mischief." I would argue that that's exactly what we are debating today, and the tools are available to take another step towards achieving those goals. Thank you for this privilege.

DR. McCANN: If speaker 15 is here, would

they please step up to the podium?

(No response.)

DR. McCANN: I think they're not here.

That is the conclusion of the open public hearing portion of this meeting. We will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments. Dr. Sharon Hertz will provide us with a charge to the committee.

Charge to the Committee - Sharon Hertz

DR. HERTZ: Hi, everyone. So we're about to start on the questions, and I think the questions are pretty self-evident. We're going to be asking you about what efficacy data are adequate to support the benefit of EXPAREL as a nerve block and how should the studies be designed. We're going to ask you about some language for the indication, how to study the safety, and any outstanding issues that you have. Then at the end, we're going to ask whether or not there should be approval for the

proposed indication.

Now, what often happens during these deliberations is we get bogged down either because an alternate indication may be considered or something might change from what we originally had, and that's okay. We can adjust things a bit if necessary. So as we go through each question, if you need clarifications on what we were trying to ask of you, or if you think that based on the conversation we need to add some additional discussion, just let us know.

We request that you provide your expertise, your experience, and your best insights to help us find a reasonable and responsible path forward. Thanks.

Questions to the Committee and Discussion

DR. McCANN: We were now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We will start with the first question, which is, what efficacy data are necessary to adequately evaluate the benefit of EXPAREL for a nerve block? Part A, discuss whether active comparator arms should be included in future efficacy studies of EXPAREL; and Part B, discuss any circumstances where placebo-controlled trials alone are adequate to evaluate the efficacy of EXPAREL.

(No response.)

DR. HERTZ: Do I have to start calling on people?

DR. McCANN: Are there any questions about the wording of the question or understanding the question? Dr. Litman?

DR. LITMAN: All right. I'll start, Sharon.

To me, it's very simple, essentially what you had told us before. And that is for A, an active comparator arm would be necessary if the sponsor wanted to state in the label that it's better than bupivacaine or any of the local anesthetics that last a certain amount of time if they can show that unquestionably it lasts longer.

For B, discuss any circumstances where placebo-controlled studies alone are adequate, well, sure. That would be great if there was an indication for local anesthesia for a nerve block, but without the extended period. So I think maybe there wasn't a lot of comments because it was simple.

DR. McCANN: Dr. Gulur?

DR. GULUR: Thank you. I would agree with the statement just made, which is an active comparator arm would be very important if we were to say this is efficacious. I also recommend that that be done with not just single shots, but continuous catheters since that is being touted as the benefit of having this longer-acting product, which would definitely make it stronger.

DR. McCANN: Dr. Galinkin?

DR. GALINKIN: I guess I'm still struggling on what efficacy means and what predefined efficacy endpoints you would want in order to demonstrate efficacy, whether it's opioid-sparing effects, whether it's decrease in pain AUC. I don't know

what actually makes a difference or what the active comparator would be.

DR. HERTZ: Perhaps we can break that down because I think at the heart of what I'm hearing is maybe a series of questions, so I'm going to turn around and ask them of you.

What I'm hearing is that you might want to consider possibly different answers under different circumstances, so to get an indication for nerve blocks in general or should there be specific individual nerve-block indications, what data should be for either of those? What data and comparators should there be for opioid sparing?

Does that help guide the response a little?

(No response.)

DR. HERTZ: Apparently not.

DR. McCANN: Dr. Litman?

DR. LITMAN: There are six of us on the panel here who have done regional anesthesia probably for a long time. I've done it for 30 years, and you guys are all probably -- well, maybe not that many but comparable. To me, it's our

judgment, essentially, in the end.

Jeff, you and I know that when we do a regional anesthetic on a child -- and I used to do them on adults -- we know when it works because they're calm and they seem to have good pain relief, and they don't require opioids, and that's all part of just the judgment. And I know it's very tempting to ask for a difference, how many hours of opioid sparing should you have, but there is not a right answer. It's just our judgment as to whether or not this drug is useful.

DR. McCANN: Dr. Zacharoff?

DR. ZACHAROFF: Kevin Zacharoff. I think, Sharon, that we do need to peel the layers of the onion apart a little bit. I think that if opioid sparing, which we certainly heard mentioned in the public commentary, was one goal, I think that that would have to be separate and apart from anything else that I would want to look at. On the other side of the coin, I think that there is a need for an active comparator arm to show superiority, inferiority, equality with respect to

catheter-based infusions that would last as long as I would expect the EXPAREL to last after the patient is post-surgical.

With respect to circumstances where placebo-controlled studies alone are adequate to evaluate the efficacy, I actually don't think there are situations because I think there's no real such thing as a placebo-controlled trial when you're dealing with post-surgical pain management, and I don't really consider that very important. But there are probably more layers with respect to active comparator arms, if we picked at it, that we could look for beyond the two I mentioned. Thank you.

DR. McCANN: Dr. Gulur?

DR. GULUR: Thank you. In terms of outcomes, the term "opioid sparing" has been brought up a lot. I cannot tell you -- I unfortunately have heard of many such stories that we've heard today in the public comments, and yet each and every one of them touches you immensely when you hear of the adverse effect it has on the

people who have been left behind and the unnecessary lives lost due to opioids.

I think if that is an important goal -- and I don't know anyone in this room who would disagree -- then it's even more important that the efficacy of this towards that outcome be shown, and not shown in a few doses that patients then need or time to the first dose, but truly to study it longer term and say does this come down.

I'll go back to the fact that not too long ago, opioids were considered the savior, and we rushed to say that this should be approved, we need more formulations, longer acting, because the thought was that pain control was as important as it is. So given that, rather than rush to decision on the replacement for these medications, it would be the appropriate standard to say this should be looked at.

So if what we're saying is that opioid sparing is important, and by that I would mean that people don't get addicted, don't have persistent use of opioids later on, then that needs to be

demonstrated if that's the efficacy we're looking for, because as others have pointed out, the fact that bupivacaine works, we all agree.

DR. McCANN: Dr. Terman?

DR. TERMAN: It seems like we're in violent agreement here. The fact is that if EXPAREL or any other product, that it's suppose to numb an area and works better than placebo, then that is, for me, good enough unless they claim otherwise. And frankly, it seems a little bit embarassing with stated 3.5 million doses given, that what we see here the last day and a half is 95 patients that are either better than placebo or better than bupivacaine, and 337 that I would say are not clinically significant, better than placebo. That strikes me as unfortunate.

But I can't argue away the results in the shoulder study, and it does appear -- I haven't heard why we think that femoral blocks are so variable, really, even when it works so poor in terms of pain relief. But that makes me think that it's time for other investigators, clearly which is

going on out there already, to take this and try and figure out what blocks this is helpful for and worth the money, frankly.

DR. McCANN: Are there any more comments on question number 1?

(No response.)

DR. McCANN: My task is to summarize a question that's been all over the map here. The question is what efficacy data are necessary to adequately evaluate the benefit of EXPAREL for nerve block? Discuss whether active comparator arms should be included in future efficacy studies of EXPAREL. I think the majority of the committee felt that it would be preferable to include a comparator arm but not absolutely necessary.

For the second part, discuss any circumstances where placebo-controlled studies alone are adequate to evaluate the efficacy of EXPAREL, Dr. Zacharoff commented that it's almost impossible to do in post-surgical patients, patients that are having pain, but others pointed out that as long as you demonstrate efficacy,

whether it's against a placebo or comparator, that that's okay.

For the opioid-sparing question, which was sort of thrown in there, people felt that that's a separate issue. If we're going to have the sponsor say that it's opioid sparing, then they need to do efficacy studies to that point.

For the second question, the applicant has requested that EXPAREL be indicated as a nerve block to produce regional anesthesia. Discuss whether the efficacy data support the use of EXPAREL as a nerve block for femoral nerve, intercostal nerves, or brachial plexus. I guess we'll start with Part A, and we'll go on after that.

Dr. Galinkin?

DR. GALINKIN: So again, I guess one of the things that I'm trying to get past here is efficacious versus safe. It seems like there are enough of these blocks being done out there that information in the label that it's safe for nerve blocks may be useful whether it's indicated -- at

this point, whether it's indicated, I think local anesthetic is indicated for nerve blocks, whether it's in this form or not. That's the question I guess. And the question in my mind more is, is this safe to use for nerve blocks since that's the way it's being used, and that's my biggest concern.

DR. McCANN: Specifically though, do the efficacy data support the use in these three nerve blocks that were mentioned? Does anybody want to tackle that question? Dr. Higgins?

DR. HIGGINS: I just keep going back to the fact that the opioid was used predominantly amongst the subjects, and I can't get past that fact. It is true that a placebo study would be very difficult post-acute surgical procedure, but the fact that it was overwhelmingly used by the subjects is something I just can't get past.

I'm also having trouble -- and maybe this is unrealistic, but the 1601 and 1602 studies were such small samples. I feel like we need more data to better assess the efficacy of this medication, but I agree with Dr. Galinkin that safety is one of

my biggest concerns with this medication.

DR. McCANN: Dr. Craig?

DR. CRAIG: Yes, I think there were a couple of examples in these studies where there was efficacy. I mean, it wasn't perfect. There are two studies of similar design but different outcomes. Femoral, it's happenstance. Maybe its patient population could be a figment of the data collection, a lot of variables there. I think in two of the four, the data's pretty clean and pretty straightforward in my opinion, and the other two I don't think is supportive.

DR. McCANN: Dr. Porter?

DR. PORTER: One of the issues that I have is the fact that it's being used already for this and it's not approved. I had a knee replacement. Actually, Dr. Mont who spoke here is my surgeon. I didn't know he was coming. And I had a knee replacement. I've had multiple surgeries for cancer, for arthritis and everything.

In September of 2016, I had this knee replacement done, and he told me he was going to

give me a new drug that's supposed to help. And from what I remember, I still went home with narcotics, but I don't believe that it was as difficult to come off of them as it had been before, but that's just my thing. But the thing is is that I was given it even though I wasn't in a clinical trial.

Let's say that we don't approve the relabeling, are doctors still going to use it?

DR. McCANN: Dr. Zacharoff?

DR. ZACHAROFF: Thank you. A couple of issues. Just going back to the placebo-controlled study, obviously we could do that kind of study, but we would have to measure how often rescue medication was necessary and use that as a way to call it a placebo-controlled study.

With respect to 2A, unless I missed something, I did not see efficacy data that supported the use in intercostal nerve block. I heard some theorizing as to reasons why the data doesn't support it as is and maybe some ways that it could be studied with volume enhancement and

more spread of injection of different nerves, but I did not see that data supported that for me.

With respect to the nerve block for the femoral nerve, what concerned me most was the idea that there was mention of the fact that in certain patient populations where early ambulation and early discharge are desired, this could be a contraindication using the medication. So that seems a little bit contradictory to me, despite a lot of the anecdotal information I'm hearing. It leaves me wondering whether or not we're blurring the lines between anesthesia and analgesia here.

I'm wondering if in some cases there are some populations of patients who are ending up somewhat anesthetized as a result of the delivery of this drug, which is what it is. It's an anesthetic as opposed to it just being an analgesic. But certainly from just purely a pain rating perspective, I think femoral nerve, yes, and with respect to brachial plexus, I would say yes as well. Thank you.

DR. McCANN: Any other comments? Dr.

Shoben?

DR. SHOBEN: Thanks. I'd actually say no, not really for any of the above just because there's sort of wide variety of possibilities. And yes, the brachial plexus data looks great, but so many of the others look less impressive, and there's so much variability between patients that I would really like to see that repeated before I had real confidence in efficacy, even at the brachial plexus. And I think that's where the strongest data were.

DR. McCANN: Any other comments about this? Dr. Gulur?

DR. GULUR: I would also support what has just been said. There is efficacy data for the femoral nerve in one study and the other study contradicts that. The intercostal nerves, we have not seen anything to support efficacy. The brachial plexus study is probably the strongest in terms of showing efficacy and a difference of some kind. But again, the question mark of if it's repeated and is it reproducible given the other

contradictions.

DR. McCANN: To summarize, there were concerns about the studies in and of themselves that they were small, that there was an awful lot of opioids being used, and that the panel would like to see them replicated. In terms of efficacy, I think most of the panel felt that the brachial plexus study showed the most efficacy, that one of the femoral studies did show efficacy, but then there are broader concerns about falls and ambulation even in the setting of the femoral nerve block, and that the intercostal nerve study did not show any efficacy. Also, concerns were brought up that this drug is already being used for nerve blocks, and we should be concerned about off-label use.

I'm going to start with the next part of this, Part B. Discuss whether the data support any of the following: a broad indication for a nerve block, individual nerve-block indications, or no nerve-block indication. This is basically the core question, so I would like to hear from

everybody if possible.

Dr. Craig?

DR. CRAIG: Thank you. Yes, I think they do. I think in two cases, in my opinion, that being the femoral and the brachial plexus data. Again, the femoral is not perfect, but I think that of the two, in my opinion, there's enough evidence to support it as a narrow indication to be approved in those two settings.

DR. McCANN: So that would put you as two --

DR. CRAIG: Correct.

DR. McCANN: -- individual nerve block.

DR. CRAIG: Correct.

DR. McCANN: Dr. Litman?

DR. LITMAN: Thank you. I could be wrong, but, Sharon, can you confirm? Have we ever had a local anesthetic approved for an individual nerve block before? I don't think so. Has there?

DR. HERTZ: We really haven't had a local anesthetic approved for any of this --

DR. LITMAN: So even a nerve block --

DR. HERTZ: -- in our modern times. Right now, I don't think there are individual ones.

DR. LITMAN: So local anesthetics have only had labeling for local anesthesia in a sense.

DR. HERTZ: More or less. There's been some variability. We've had some things for dental and other things like that.

DR. LITMAN: If that's the case, I would be strongly opposed to labeling any local anesthetic for individual nerve blocks. You're just opening up a potential for just such a slippery slope for the future.

The problem with these studies, as we've seen here today, local anesthesia is not like -- especially when you're trying to get a nerve, it's not the easiest thing in the world, even when you use ultrasound. There are so many different results that could happen. Every nerve in the body is a little bit different, the approach.

As I sat here the last day and a half thinking about this, if you think about which

nerves can you really isolate without it also being a little bit of an infiltration or a field block? There are hardly any. The only one I could think of, really, was maybe an interscalene. Maybe someone else can think of another one. So it's really hard to do these studies, and it's really hard to -- there's so much -- someone just cut me off?

(Laughter.)

DR. LITMAN: I've got it. There's just so much individual variation in the way we do things, and these studies bore that out. There were so many different ways that these patients got all their blocks, whether or not they were in the United States or Bulgaria. There's so much variability, and it would be very difficult and an incredible burden on both the sponsor and the FDA to focus that so narrowly.

I personally don't -- I didn't think any of the studies here -- I would completely echo some of my colleagues here, Abby and Padma, but it shouldn't be just for one nerve.

DR. McCANN: I'll weigh in. I actually think the brachial plexus study showed efficacy. I at this point don't see how I could give a broad indication for a nerve block, so I would be somewhere between 2 and 3, either no nerve-block indication and individual nerve-block indication.

DR. GALINKIN: Jeff Galinkin. I'm with Ron, and I would not give an indication for specific nerve blocks. I would put safety data in the package insert and dosing information, but I would not give efficacy. I don't think that they've demonstrated adequate efficacy in the small trials that they have.

DR. McCANN: Dr. Terman?

DR. TERMAN: And I agree that if you want off-label activity, just try and put an indication for just one nerve block. And in some ways I think maybe that's the reason we're seeing what we're seeing. I agree with one of the public speakers, the TAP block is not infiltration of the wound; it's a block. I think that it's already approved for a nerve block in the TAP block, and I think it

may be difficult to put the genie back in the bottle.

DR. McCANN: Dr. Zacharoff?

DR. ZACHAROFF: I would have to agree with previous comments, echoing what Dr. Litman and Dr. Galinkin and Dr. Terman said. I don't think a real-world experience would ever include an indication for certain nerve blocks and not others. I guess what I have to think about at the end of the day is the safety information to guide me.

I think that if I try not to think about efficacy, which is a strange thing to say, I do feel comfortable with respect to the safety. I think with the number of uses of this medication despite the variability of concentrations, I do feel comfortable with the safety. So I think it's not realistic to limit it to individual nerve-block indications, and I think that the safety data that's been presented would guide me to support broad indication for nerve blocks.

DR. McCANN: Any other comments?

(No response.)

DR. McCANN: Basically, the panel were leaning, a think a preponderance, towards no nerve-block indication because doing an individual nerve-block indication would be very difficult for practitioners to follow. It's never been done before, so it would be not advised; although there is some dissent and at least one person on the panel feels that the drug is very, very safe, which would support a broad indication for a nerve block.

Part C, if we do not have data adequate to support any nerve-block indication, describe the data that would be necessary to support this indication.

DR. HERTZ: Hi. It's Sharon. As you ponder this -- this is really important and we're listening very intently. So as you approach what data would support some type of indication, please let us know how you would integrate both the positive and the negative studies.

Do you know what I mean? If you don't believe in a general block, which individuals? If you believe that individual nerve-block indications

are problematic and it should only be general or nothing, then how do you integrate the negative studies?

DR. McCANN: Dr. Terman?

DR. TERMAN: I was kind of hoping that the sponsor would help me out there. In fact, that was one of the first questions I asked was how do you explain femoral works sometimes and doesn't work other times? I will say that from a clinical standpoint, the shoulder blocks are really nice because they get rid of all the pain, and that's certainly not true of a femoral block for knee arthroplasty, so maybe that's relevant.

Clearly, we don't know what we're doing with this drug, and maybe it's the fact that when you look on an ultrasound at a femoral nerve, it's really more a region than it is a spot. I think I've heard somewhere, although not the last day and a half, that this drug really doesn't diffuse like a normal local anesthetic, that it tends to stay where it's put almost like a device, and maybe there are certain nerves that are going to be

better blocked than others more consistently. I don't know.

I'm not sure that's the question we are asking today, to know exactly why -- in order to show efficacy, I don't know that you have to know why it doesn't work in every single patient, for instance.

DR. McCANN: Dr. Litman?

DR. LITMAN: I'm not sure I can say it better than Dr. Terman. It was sort of similar to what I was thinking, but I'll just target it a little bit more. If we've never really given a label for a particular type of use -- in my mind, there are like three kinds of uses. There's infiltration or subQ, there's nerve block, and then there's central like epidural or spinal. Maybe that's four.

If there haven't been previously specific labeling for one of those routes, then I'm a little bit stumped as to why we should start now. We've all, the six of us, have been doing all four of those for many years with hopefully great success.

Most of the time they work; sometimes they don't of course. But once you show that a compound works and provides numbness, anesthesia, whatever you want to call it, then that should be fine, and then it should be up to the clinicians after that how to use it.

Now, that's not saying -- I think we still have the responsibility for safety data of course. But efficacy, I'm not quite sure I understand why we would need a particular label for a particular route, unless I'm missing something like insurance coverage. But if it hasn't for lido and regular bupivacaine and ropivacaine --

DR. HERTZ: Right, but I don't think we had the same clinical study data to work with because we thought about things differently. Now we have a variety of studies and a variety of outcomes, and we're trying to make sense of that so that it is properly reflected in the label.

DR. LITMAN: Yes, that's really hard, but that's why we're here. I get it.

DR. McCANN: Dr. Gulur?

DR. GULUR: I actually think that the grouping of the studies is actually quite good. I like the fact that there is upper extremity with the brachial plexus, lower extremity block with the femoral nerve, and you have the intercostal, which is, really from a safety signal standpoint, especially important because most vascular and the highest amount of uptake from there. I actually like that combination.

I think the issue here is that the data is confounding; you don't see enough. And that could be a factor of the various things that they've pointed out were shortcomings. But then if they were shortcomings, maybe that needs to be fixed. Maybe there needs to be a design where having learned the shortcomings, design it so that those are not ongoing confounders for one thing.

The second thing would be the active comparator. Having that would truly demonstrate more efficacy than placebo alone, which I still feel is more does bupivacaine work or not, so that would be useful.

As far as the other parts are concerned, I don't think we should be doing every single nerve. It's nearly impossible to do every single nerve, but representative, upper extremity, lower extremity, intercostal I thought was a reasonable mix. I would just like to see maybe a larger study, controlled design where -- even the sponsor has admitted they had serious concerns about how these studies were done, the experience of investigators amongst other things. So they seem to have really good learning points here to design this better and to be able to demonstrate efficacy better in the next round.

DR. McCANN: Dr. Galinkin?

DR. GALINKIN: From a practical point as an anesthesiologist, I think we all -- I'm with Ron in that there's three categories of blocks, and all we really care about is what's written on the bottle, whether it says not for intrathecal use, not for epidural use, or not for infiltration, and the majority of anesthesiologists are going to look at that. The efficacy data, from their perspective,

it's either long-acting or short-acting local anesthetic.

From an efficacy point of view, in a lot of these studies, it's very complicated because they're talking about -- one group's actually getting this ERAS type, enhanced recovery after surgery type thing with this nerve block and the other one's not. So oftentimes it's very difficult to sort out, in many of the other studies that they presented, what's actually due to the block, what's due to their multidisciplinary or multidrug regimen.

What's happening I think now is every day we walk in the operating room, the resident or whoever you're working with is doing a smaller and smaller nerve to block. So as they said, they've already switched from the femoral nerve to adductor canal and something else, and I think honestly it's getting harder and harder to do these studies and show that one's better than the other. So I agree with Ron. It's very difficult to support a single-nerve efficacy, a broad indication or not,

in my opinion.

DR. McCANN: Dr. Zacharoff?

DR. ZACHAROFF: I don't think that the efficacy data is adequate to support any nerve-block indication. I think that some good outcomes and some of the studies don't in my mind do what I think I expect the FDA to do, which is look at safety, look at efficacy and designated pain models, and then let people go out there and do what they're going to do, which is what I think is going to happen.

But if I consider the efficacy data to be inadequate except for the shoulder study to support a nerve-block indication, then what I think I would require would be study without concomitant infiltration in addition to the nerve block because I think that that muddies the water even more; comparison to catheter-based techniques, as I mentioned before, for similar periods of time. And as we just heard, comparison to the enhanced recovery after surgery approaches so we could factor those out as variables, and factor out as

much else as we could.

We heard age discussed here and demographics. I think certainly we anesthesiologists know that age is an important determinant of pain ratings post-surgically, and some age groups are more prone to postoperative pain, and respond better, and have higher opioid needs than others. So I think I would want to see some higher level of standardization of the patient populations from a demographic perspective as well. The surgical procedure in and of itself doesn't cut it for me because I've done anesthesia for total knee replacements in 49-year-olds, and I've done the same for 79-year-olds, and it's not the same course.

DR. McCANN: Dr. Shoben?

DR. SHOBEN: I would agree with some of the comments about the diversity of the sites, that you can't possibly study every single indication, but what they actually did in terms of the shoulder and the knee and the intercostal, it was a really nice mix of that kind of thing.

The question was about how would you go about including some of the negative studies and trying to make sense of everything if there are more studies. I think there are two approaches. One is just look at the learning curve and say we've learned from these studies, these are some of the challenges, and therefore we don't think this study is representative of how it would be used in actual clinical practice.

You could throw it out in a sense to say this is learning about what's going on. And then some of the others, you could include in a meta-analysis so that there's not all data loss by saying this is a negative study and this is a positive study, but instead all the studies are contributing to an overall efficacy profile.

DR. McCANN: Any other comments?

(No response.)

DR. McCANN: We're supposed to answer, if you do not find the data adequate to support any nerve-block indication, describe the data that would be necessary to support this indication?

The committee found that the data that was presented, although it was great that it represented the upper extremity, lower extremity, and a truncal area, the data was found to be conflicting and confounded with many shortcomings. Suggestions to improve the data would be to make the studies larger, to include an active comparator to see whether there's efficacy, and basically replicate the studies.

People also mentioned that using a catheter infusion would be a good comparator in that nerve infiltration may be a confounder that would be good to not use in a future study. It was also mentioned that standardizing the patient population may make the data a little bit more understandable.

Dr. Zacharoff?

DR. ZACHAROFF: The only thing I would correct with respect to what I said was soft tissue infiltration, not nerve infiltration.

DR. McCANN: Absolutely. Sorry.

To get to question 3, what safety data are necessary to adequately evaluate the risks of

EXPAREL for nerve block? Part A, discuss whether active comparator arms should be included in future studies of EXPAREL.

Dr. Litman?

DR. HERTZ: Hi. It's Sharon again. Because the group is so chatty, just to make it perhaps a little easier to respond, perhaps we could have people opine on all three. Maybe you could read all three subgroups into the record, and then just opine more generally.

DR. McCANN: Part B, discuss whether there are circumstances where placebo-controlled studies or open-label studies are adequate to assess the safety of EXPAREL.

Discuss whether the safety data submitted are adequate to characterize the safety profile of EXPAREL.

Dr. Litman?

DR. LITMAN: Thanks. A and B are sort of the same as what we talked about for efficacy. But the other point that I should bring across is that as far as doing an active comparator versus

placebo, I think it just depends upon your own practice and the center's practice for equipoise. Equipoise means, let's say you have a practice where you always do a block for this particular surgery, than I don't think it would be the right thing to do comparator versus placebo, whereas if your practice was that it varied and some people didn't get a block, then it would be okay to use a placebo.

I wanted to make that point of it depends upon individual practice and the centers that do these research.

C, from everything I heard here, I'm not convinced that we have adequate safety data. I'm very alarmed at the signal of the increased deaths compared to the percent of vials that have been sold. I'm sure -- well, I shouldn't say I'm sure. I think it's very possible due to bias and reporting with a new drug, whereas LAST or systemic toxicity from local anesthetics with the old drugs are probably so common now that they're not reportable to the FDA, is my guess. But I do think

it's incumbent to show that there isn't an increased likelihood of local anesthetic toxicity and a decreased likelihood of being able to rescue with intralipid.

I think those kind of studies would be relatively easy to do. I know no study's ever easy, but I don't see why you can't take apology to the animal rights folks, and to take an animal model and see what doses it takes between comparators and EXPAREL to see what dose causes cardiac arrest and then use some dose that gives you toxicity and make sure you can rescue with intralipid. Imagine if you couldn't. That would be something we would never want to put out on the American public.

DR. McCANN: Dr. Shoben?

DR. SHOBEN: I think that the safety depends on what your comparison is to. If you want to compare safety based on an active comparator, then you should be efficacy based on active comparators. So if treating someone with a nerve block for their knee replacement or knee arthroplasty results in

more falls, then that would be easily compared using an active comparator, but then you have to compare efficacy to the active comparator as well.

I'm actually most concerned here about the safety with the falls and that population in the sense of you saw that signal in one study and then you saw it in the second study. We migt be willing to tolerate it if you in fact had efficacy over placebo, but you can't really sort of say, hey, it's better than placebo and it's not any worse than the active comparator for safety.

DR. McCANN: Dr. Zacharoff?

DR. ZACHAROFF: I actually have a question. I'm wondering if this is the part where the opioid-sparing discussion starts because it is a discussion of safety to me in some way. And if we think about the idea of opioid sparing as with the intention of using lower opioid doses, diminishing opioid related adverse effects, then to me that becomes part of the safety discussion. So that's a question.

DR. HERTZ: I think we meant it as

demonstrating the safety of the product.

DR. ZACHAROFF: Okay.

DR. HERTZ: But feel free to expand on anything you want.

DR. ZACHAROFF: So I agree with what Dr. Shoben said with respect to falls. I think that I would need some kind of study to show me stronger information about that because we know fall risks in hospitals are bad words to say. At the same time, I think with respect to the opioid-sparing aspect of this, as we saw in the data presented this morning, there wasn't a lot of evidence to show that there was a significant decrease in the utilization of opioids. But on the flip side, I'm not sure as part of these other expedited recovery after-surgery programs, that some of those things don't play into this as well.

I think we need to discuss this in that context because we hear a cry, obviously, for people to say we need non-opioid solutions to add to the multimodal regimen. Bupivacaine is not a new drug. The liposomal release, the DepoFoam is

not a new release mechanism, and from that perspective, I don't have as many concerns as Dr. Litman does. But from the opioid-sparing perspective, to me that's where all of this really lies. How much are we willing to put on the table to think about to diminish the uses of opioids, to diminish the use of prescribed opioids, and to manage those patients appropriately?

So I would encourage us to talk a little bit more in depth about the whole idea of opioid sparing, what it means to us, what we would consider to be meaningful in terms of opioid sparing, and to hone in on that a little bit.

DR. McCANN: Dr. Higgins?

DR. HIGGINS: This is not in response to your comments, Dr. Zacharoff. I'm really guided by the data on AEs, and that was really what I honed in on immediately: the falls, the sensory motor function with the extended period of numbness, and the fact that they were claiming to meet milestones with PT at a faster rate. And the LAST fatalities, I just couldn't get over them.

These all to my mind were directly affected by age, so I'd like to see increased data collected that would address these issues in particular and make me feel more confident about the safety of the medication.

DR. McCANN: Dr. Porter?

DR. PORTER: Yes. I think if we're going to bring up opioid sparing that we need to have some proof of it, whatever we want to define as. But we need to define it, and there need to be studies that actually demonstrate it because to say that it's opioid sparing would be to me like saying that abuse deterrence actually is abuse deterrent. So we need to be sure of what we're saying.

DR. McCANN: Dr. Galinkin?

DR. GALINKIN: Talking about safety, it's almost impossible to do the safety study without a huge amount of patients. And you might thing that this is impossible, but in pediatrics, we've established the Pediatric Regional Anesthesia Network. We've collected about 115,000 blocks with postoperative follow-up and information in 11 years

with minimal cost. And that's the type of study that needs to be done in adults here to get registry information to compare incidences of LAST so that you can compare regular local anesthetics to the long-acting anesthetics, as well as other complications.

I think the issue with opioid sparing, I don't think that is really -- although it's an interesting safety question, I don't think it's a safety endpoint that's going to be very easy to solve. But I think it would be both in the company and the FDA's interest to consider a registry for blocks.

DR. McCANN: Dr. Terman?

DR. TERMAN: Yes. In terms of opioid sparing, I think if we're going to talk about opioid sparing -- and I didn't really pay too much attention to that, but clearly if you're going to talk about opioid sparing, you're not going to want to compare that to the placebo. I'm not sure too many people would think that placebo causes a lot of opioid sparing. There you really do need an

active comparator, and the fact that despite recommendations for active comparators, that has not been what the sponsor has done except with the investigator initiated studies. I'm not sure that opioid sparing was the plan at all.

My concern about safety, again, in terms of falls, you'd like to know how does that compare to other active comparators. But what clearly does not compare to other active comparators is the delayed onset of the pharmacokinetic peaks. I'm fortunate that in our institution, I'm able to set the policy, so no local anesthetics are given within 96 hours after EXPAREL.

I was disturbed to hear that's not the way the current product insert is interpreted, that somehow lidocaine toxicity in addition to the EXPAREL is less important. I definitely think that that needs to be changed. I don't know how to do that at this stage, but that should not say bupivacaine within 96 hours. That should say local anesthetic. And I even had to take a step back and say, no, it's okay to give some intradermal

lidocaine for an IV start. But again, people need to be thinking about that because that is very different than what we think of in terms of systemic pharmacokinetics after a normal nerve block or even an infusion.

DR. McCANN: Are there any more comments? Dr. Craig?

DR. CRAIG: Thank you. Just a comment about opioid sparing. In my opinion, it's not really a very valuable clinical outcome without any kind of context and tied to something else. So we need some kind of other calculus in looking at dose in relation to either pain intensity or dose in relation to functional outcomes. There has to be a relationship between the two, so in essence making an X/Y graph and looking at the relationship between the two.

You could just simply give Ativan as a post-surgical analgesic and have less opioid consumption in the Ativan group versus an opioid alone. That's just not a very reasonble outcome. So again, balanced either to pain intensity or

functional outcomes, or side effects, there has to be some kind of triangulation or relationship between that to provide context.

The pain intensity in my opinion in these particular studies was enough. I think the nice additive effect would be the opioid-sparing effect in a functional outcome. The opioid sparing is a nice additive plus, but in my opinion it really is not that meaningful.

DR. McCANN: Dr. Gulur?

DR. GULUR: I'd like to reiterate some of the things that have already been said in regard to safety of the product itself, concern for the falls, and I do support what Dr. Litman said. It would be nice to have information on a study that showed that intralipid would work in this and easily, or at least potentially, be designed to give us that information.

I'm a big believer that opioid sparing, whether it's been studied or not, has definitely been the topic of discussion, not just from the sponsor or committee, but also from the public

speakers. It's an issue of great concern to everybody, so it would be nice to study that. Again, longevity will matter, not within the first few days but whether persistent use is in some way affected by the use of these products per se.

Lastly, I would just like to reiterate what Dr. Terman said in terms of the FDA existing label. I address this to the sponsor and the FDA that it is subject to misinterpretation because it specifically says bupivacaine should not be given. And since I heard very clearly, as did all of us, from the sponsor that that was not their intent, they meant for that to say local anesthetic, it would be good to have that corrected. Thank you.

DR. McCANN: Any other comments?

(No response.)

DR. McCANN: I'm going to basically reiterate what Dr. Gulur just said. It was mentioned that if further studies are to be done, that any comparators should be those that are standard of care in your institution in order for equipoise. There was significant safety alarm

about the increase in deaths associated with this drug, although it was suggested that part of that may be due to bias in reporting, and that there was a need to prove that the drug when it's overdosed, the effects can be rescued with intralipid. A fair percentage of the committee have concerns about the increased level of falls. So all those safety issues need to be dealt with.

A lot of discussion went on about what exactly opioid sparing means, and I think the FDA could help us in the future with maybe delineating what that means. At least one person pointed out that just having a decrease in opioid use shouldn't be the definition of opioid sparing and that we need other metrics in order to consider something opioid sparing. The suggestion was made to develop a safety registry for this drug and other drugs. And finally, it was suggested that the existing labeling can be easily misinterpreted. So if nothing is done today, but altering that labeling, that would be a positive.

DR. GALINKIN: I just want to point out from

a registry point of view that this has become a lot easier down at most institutions or with EPIC [ph], and if FDA partners with one of these large recordkeeping systems, this type of information shouldn't be very difficult to get.

DR. McCANN: Thank you. Question number 4. Please discuss whether the data are adequate to support a change in the proposed indication from administration into a surgical site to produce post-surgical analgesia to a single-dose infiltration to produce local analgesia.

DR. McCANN: It's a talkative group. Dr. Litman?

DR. LITMAN: I'll start again, Sharon. I think everything -- this is my own personal opinion. Based on everything I've heard here today, the answer is no. The discussion already happened.

DR. McCANN: Dr. Zacharoff?

DR. ZACHAROFF: I would agree with Dr. Litman. I'm really worried about changing the wording from "post-surgical analgesia" to "local

analgesia" because it seems to imply that people might use it for other uses other than post-surgical uses, and I wouldn't want to see that happen. I'm not sure that that adds a benefit unless there's some thinking that this would be used in a non-post-surgical way.

DR. McCANN: Dr. Craig?

DR. CRAIG: I'll jump in. For me, I think the word "post-surgical" here is critical, and whatever the final iteration is has to include that word I think based on what the studies were. I do support specific site indications, and maybe that's just the wrong strategy, but again, my opinion would be if you don't have data for other areas that we shouldn't be using there. And I understand the concerns about using it off label, but in my opinion, sitting here on this committee in support of it being used I'm not comfortable with it. There are other areas where it's either been shown to be not helpful or we just don't have data.

DR. McCANN: Dr. Galinkin?

DR. GALINKIN: I guess my problem is, again,

unless you tell people not to use it as single-dose infiltration, they're going to use it. The single-dose infiltration, I'm not for changing it, but I'm concerned that none of the studies that were really presented were from dentist office where they're administering this or something like that, which I think is what everybody's worried about.

My concern would be if you change it from one to another, that's what you're going to do, but the question is should you say not for single-dose infiltration and only for post-surgical analgesia.

DR. McCANN: Any other comments? Dr. Terman?

DR. TERMAN: I might be a little different on this one, although I agree that post-surgical analgesia is what we've seen in terms of any data. A single-dose infiltration rather than the administration into the surgical site certainly captures the TAP blocks better, which was a more recent addition to the approved used of thid drug. And I don't know all the details about how that

came to be, but again would say that administration into the surgical site does not necessarily describe a TAP block.

DR. McCANN: Any other comments? Dr. Zacharoff?

DR. ZACHAROFF: I think some amalgam of the two statements would fit, which would be single-dose infiltration to produce post-surgical analgesia. And that takes the best of both in my opinion.

DR. McCANN: Any other comments?

(No response.)

DR. McCANN: First, the committee was a resounding no. Dr. Terman spoke and suggested that actually single-dose infiltration to produce local analgesia is already one of the indications but is not labeled as such, and then Dr. Zacharoff actually changed the discussion into a combination of both statements. So I don't know what the FDA wants to do with that.

For question number 5, please discuss any outstanding issues with this supplemental NDA that

warrant additional studies. And if so, should these studies be conducted before or after approval? Dr. Galinkin?

DR. GALINKIN: Again, I think that a postmarketing registry is going to be very important to distinguish whether this continues to have a higher incidence of LAST than other local anesthetics. And the only way to do that is to do a broad safety registry across a large population.

DR. McCANN: Dr. Higgins?

DR. HIGGINS: Very succinctly, I would say yes. I feel like more studies are needed before approval.

DR. McCANN: Dr. Zacharoff?

DR. ZACHAROFF: If I look at this question, I think if I were an opioid, what discussion would be having. And the answer we'd be saying is yes, we need additional studies in order to support this supplemental NDA that demonstrate efficacy, that demonstrate the issues of safety and so on and so forth. Those are my outstanding issues, and if we choose not to let the non-opioid quality cloud our

judgment, then the answer has to be yes in my mind.

DR. McCANN: Dr. Terman?

DR. TERMAN: I am a big fan of local anesthetics, and if EXPAREL can get people who haven't been using local anesthetics to use local anesthetics, that's wonderful. I'm all in favor. But one of the things that concerns me the most, and this hits home to my practice, is what I talked about before, that when you use EXPAREL, it ties my hands for using other local anesthetics for several days and turns me into a non-opiate sparer but an opiate purveyor because all I have -- really, high-efficacy analgesics is up and up on the opiates, and that is a risk in a way. That is a problem with not comparing the true local anesthetic comparator because if you use one -- it's not like giving gabapentin and then I can always give something else if that's not sufficient. This is something that if I give and it doesn't work, I'm out of luck. I've got to go to something completely different, and unfortunately, completely different is just the

opposite of what we heard today from the public. So this is a really important issue for me, personally.

In terms of supplementing the NDA, obviously additional studies as has been said, although I do think the efficacy has apparently been demonstrated, at least in some blocks. The comparator with the active comparison is really important to figure out where this drug positions itself in the landscape.

DR. McCANN: By more studies, you mean pre-approval or post-approval?

DR. TERMAN: Well, in the last question, we didn't talk about the specific indication for nerve blocks. I'm not sure that it says that in this question either, but I would say that need to be done. Whether it's pre-approval or post-approval is less important to me.

DR. McCANN: Dr. Shoben?

DR. SHOBEN: I think the outstanding issue for me -- and it's been hit on a couple different times, but I just wanted to make the point myself,

that this issue of marketing in a possible opioid-sparing medication, you absolutely need the longitudinal data to show that they're off opioids sooner, that there's less addiction, there's less long-term use. There's that sort of thing. And I would be fine with that coming post-approval. I just want that to be clear that you can't possibly approve this opioid sparing and sell it as such just based on the differences that we've seen in the clinical trials.

DR. McCANN: Dr. Porter?

DR. PORTER: I think definitely more studies need to be done, but I'm not sure that the issue today is about opioid sparing. They're asking for the supplemental NDA to just change what we've already read. I don't think they're asking for it to say opioid sparing. I think that's a different issue. But I think that more studies need to be done, and I'm okay with either post- or pre-approval.

DR. McCANN: Dr. Craig?

DR. CRAIG: In regards to this sNA, I don't

think we need more studies in my opinion. I think that there's enough studies to help guide this decision because then I would challenge the people who say that we need more studies what kind of studies do we need. The active comparator studies would be nice. And if you look at most of the active comparator studies, there's no difference between EXPAREL and active comparator in the regular release bupivacaine.

That's a specific issue that clinicians can help to digest and to understand whether they need to use it in their practice or not. That's not really the question. The questions is do we need more data to support this expanded indication. My opinion, no.

DR. McCANN: Are there any other comments?

(No response.)

DR. McCANN: Summarize. Most people felt more studies were needed. Some people felt it should be done pre-approval; others thought post-approval especially for the indication for opioid sparing. The concern was brought up that's

a little bit tangential, that one of the issues with failed EXPAREL block is that it turns the physician into an opioid purveyor. That concern could maybe be mitigated by doing active comparator studies, which would demonstrate whether you were purveying more or less with EXPAREL.

I think we're getting ready for the voting stage. If there are no further discussions on this question, we will begin the voting process. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed the vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next we will go around the room, and each individual who voted

will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed.

The question for all of us is, do the efficacy, safety, and overall risk-benefit profile of EXPAREL support the approval of the supplemental application to add an indication for nerve block to produce regional anesthesia or any individual nerve-block indications?

Are there any questions about the question? Dr. Craig?

DR. CRAIG: I hate to ask, but could we just modify the question a bit to include the language Dr. Zacharoff proposed? I think as written, I'd say no, but if it could be modified and tweaked a bit, then I think the answer changes to yes.

DR. HERTZ: So we're trying to get here about the nerve-block piece rather than the first part piece. Does that help? It doesn't look like it. The way one could rephrase this is do the data

submitted in support of the request for a nerve-block indication support adding that on to the indication as an additional indication.

DR. CRAIG: Okay.

DR. HIGGINS: Forgive me. I didn't follow that. Could that be repeated, maybe stated more declaratively?

DR. HERTZ: What we're trying to ask for the vote is -- time out.

(Pause.)

DR. HERTZ: I'm just going to fill a little space while they take care of posting that.

It's really been interesting to hear the response to our questions, and I think what it reflects is the difference between being immersed in something and coming in and trying to understand it when you're not immersed in it; because we really think these questions are so crystal clear when we write them, and you frequently school us that it's not the case.

(Pause.)

DR. McCANN: It's a much shorter question.

That's great. Do the data submitted support approval of an additional indication for nerve block?

Dr. Zacharoff?

DR. ZACHAROFF: I would think the word "postoperative" would need to be in there.

DR. McCANN: What would you suggest, Dr. Zacharoff?

DR. ZACHAROFF: It's an additional indication for nerve-block use for bupivacaine analgesia. I'm just trying to clarify.

DR. HERTZ: Yes.

DR. McCANN: So is everybody ready to vote? Let's vote.

Everybody has voted. The vote is now complete.

(Pause.)

DR. McCANN: Somebody had an emergency bathroom break.

(Pause.)

DR. HERTZ: We're going to take a -- we'll go with a five-minute break just to kind -- just

make sure everyone's back because then we can actually take the vote, and do one more round, and let you all --

(Laughter.)

DR. HERTZ: Did we lose anyone from the table? Never mind; no break. Skip the break.

(Voting.)

DR. McCANN: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. We'll start with Dr. Shoben.

DR. SHOBEN: Abby Shoben. I voted no for most of the reasons I've already said. I don't think the efficacy data are there. Yes, the brachial plexus data looks promising, but given the amount of variability in the other studies and the amount of variability in the PK data, I'm not convinced of the efficacy. And in addion there are some safety concerns that I would like to see more data on before approval.

DR. CRAIG: Dave Craig. I voted yes, I

think primarily because of how I stated before. I think that the data is there for at least two of the areas of block based on the studies that were submitted, so that's why I voted how I did. I thought there were some concerns about safety, but I'm not overly concerned that this would add significant safety to prohibit an expanded indication.

DR. LITMAN: Ron Litman. I voted no because I wasn't convinced of the data that was presented here at the FDA of both efficacy and safety. I think EXPAREL's going to be an excellent local anesthetic, and I would echo Dr. Terman's comments before. It's just a shame that we didn't see the data here today. But I think there will continue to be either pre- or post-label clinical studies that will be convincing, and it will, probably as long as the safety data pans out, be a very widely used local anesthetic someday.

DR. McCANN: Mary Ellen McCann. I voted no. Probably the main reason is I had safety issues. I actually thought that they did demonstrate some

efficacy, so if I didn't have the safety issues, I probably would have voted yes. But I was concerned about the falls, the signal of deaths, and no data about rescue medications.

DR. GALINKIN: Jeff Galinkin. I voted no. Again, I also had a concern about the efficacy and some of the safety data. Further, in the future, it would be nice to see some pediatric dosing information as well.

DR. HIGGINS: Jennifer Higgins. I voted no for the reasons I stated previously.

DR. PORTER: Laura Porter. I voted yes.

DR. TERMAN: Greg Terman. I voted yes with the proviso that the current restriction on bupivacaine within 96 hours was generalized to all local anesthetics, that some preclinical lipid emulsion therapy studies were done to make sure there wasn't interaction between the liposomes and the lipid emulsion, and finally, an active comparison in the brachial plexus study to show more prolonged use or benefit.

DR. ZACHAROFF: Hi. This is Kevin

Zacharoff. I voted yes, and I would echo Dr. Terman's comments with respect to other studies. At the end of the day, I think being that this was a medication that had already been approved, I think there was enough information for me, from a safety and efficacy perspective, to vote yes. With respect to the falls, I think a lot of it has to do with what's done on an institutional basis with respect to people who are at fall risk and not the medication itself.

DR. GULUR: Dr. Gulur. I voted no for reasons already stated by my colleagues and with the same recommendations that my colleagues to my left made even though they voted yes, that further studies are required.

DR. McCANN: We're not going to take a break now, right? We're ready to adjourn?

DR. HERTZ: Yes.

DR. McCANN: Are there any other questions for the FDA or other comments for the FDA?

(No response.)

DR. HERTZ: With that, I will thank you-all

again. Again, we really appreciate it. We know how busy you are, so thank you and safe travels home.

Adjournment

DR. McCANN: Panel members, please take all your personnel belongings with you as the room is cleaned at the end of the day. All materials left on the table will be disposed of. Please also drop off our name badge at the registration table on the way out so they may be recycled. We will now adjourn this meeting. Thank you.

(Whereupon, at 2:56 p.m., the meeting was adjourned.)