

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

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

1 **Meeting Roster**

2 **DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Moon Hee V. Choi, PharmD**

4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

7

8 **ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY**

9 **COMMITTEE MEMBERS (Voting)**

10 **David S. Craig, PharmD**

11 Clinical Pharmacy Specialist

12 Department of Pharmacy

13 H. Lee Moffitt Cancer Center and Research Institute

14 Tampa, Florida

15

16 **Jeffrey L. Galinkin, MD, FAAP**

17 Professor of Anesthesiology and Pediatrics

18 University of Colorado, AMC

19 Medical Safety Officer

20 CPC Clinical Research

21 University of Colorado

22 Aurora, Colorado

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

Jennifer G. Higgins, PhD

(Consumer Representative)
Director of Research & Policy
Association of Developmental Disabilities
Providers (ADDP)
Framingham, Massachusetts

Ronald S. Litman, DO

Professor of Anesthesiology & Pediatrics
Perelman School of Medicine
University of Pennsylvania
Attending Anesthesiologist
The Children's Hospital of Philadelphia
Medical Director, Institute for Safe Medication
Practices
Philadelphia, Pennsylvania

1 **Mary Ellen McCann, MD, MPH**

2 *(Acting Chairperson)*

3 Associate Professor of Anesthesia

4 Harvard Medical School

5 Senior Associate in Anesthesia

6 Boston Children's Hospital

7 Boston, Massachusetts

8
9 **Abigail B. Shoben, PhD**

10 Associate Professor, Division of Biostatistics

11 College of Public Health

12 The Ohio State University

13 Columbus, Ohio

14
15 **Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP**

16 Faculty and Clinical Instructor

17 Pain and Medical Ethics

18 State University of New York Stony Brook School of

19 Medicine, Stony Brook, New York

20 Ethics Committee Chair

21 St. Catherine of Siena Medical Center

22 Smithtown, New York

1 **TEMPORARY MEMBERS (Voting)**

2 **Gregory Terman, MD, PhD**

3 Professor, Department of Anesthesiology and
4 Pain Medicine and the Graduate Program in
5 Neuroscience
6 Director, University of Washington Medical Center
7 Acute Pain Service
8 University of Washington
9 Seattle, Washington

10

11 **Padma Gulur, MD**

12 Professor of Anesthesiology
13 Vice Chair, Operations
14 Department of Anesthesiology
15 Duke University
16 Durham, North Carolina

17

18 **Laura D. Porter, MD**

19 *(Patient Representative)*
20 Cancer Survivor Independent Patient Advocate
21 Washington, District of Columbia

22

1 **ACTING INDUSTRY REPRESENTATIVE TO THE ANESTHETIC**
2 **AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE**

3 **(Non-Voting)**

4 **Michele Hummel, PhD, RPh**

5 *(Acting Industry Representative)*

6 Pharmacist

7 Moss Rehab Einstein Healthcare Network

8 Elkins Park, Pennsylvania

9
10 **FDA PARTICIPANTS (Non-Voting)**

11 **Sharon Hertz, MD**

12 Director

13 Division of Anesthesia, Analgesia and Addiction

14 Products (DAAAP)

15 Office of Drug Evaluation II (ODE-II)

16 Office of New Drugs (OND), CDER, FDA

17
18 **Rigoberto Roca, MD**

19 Deputy Division Director

20 DAAAP, ODE-II, OND, CDER, FDA

21
22

1 **Alla Bazini, MD**

2 Medical Officer

3 DAAAP, ODE-II, OND, CDER, FDA

4

5 **David Petullo, MS**

6 Statistics Team Leader

7 Division of Biometrics II

8 Office of Biostatistics (OB)

9 Office of Translational Sciences (OTS)

10 CDER, FDA

11

12 **Yun Xu, PhD**

13 Clinical Pharmacology Team Leader

14 Division of Clinical Pharmacology II

15 Office of Clinical Pharmacology (OCP)

16 OTS, CDER, FDA

17

18

19

20

21

22

1	C O N T E N T S	
2	AGENDA ITEM	PAGE
3	Call to Order and Introduction of Committee	
4	Mary Ellen McCann, MD, MPH	10
5	Conflict of Interest Statement	
6	Moon Hee Choi, PharmD	14
7	FDA Introductory Remarks	
8	Sharon Hertz, MD	18
9	FDA Presentations	
10	Assessment of Efficacy Data of Studies	
11	Submitted in Support of sNDA	
12	Alla Bazini, MD	20
13	Statistical Review of EXPAREL Efficacy	
14	From Nerve-Block Studies	
15	Katherine Meaker, MS	37
16	Alla Bazini, MD	48
17	Pharmacokinetics (PK) of EXPAREL from	
18	Infiltration and Nerve-Block Studies	
19	Suresh Naraharisetti, DVM, PhD	61
20	Assessment of Safety Data of Studies	
21	Submitted in Support of sNDA	
22	Alla Bazini, MD	77

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

C O N T E N T S (continued)

AGENDA ITEM	PAGE
Clarifying Questions	91
Open Public Hearing	155
Charge to the Committee	
Sharon Hertz, MD	197
Questions to the Committee and Discussion	198
Adjournment	260

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

1 DR. McCANN: Hello. Good morning. I would
2 like to remind everyone to please silence your cell
3 phones, smartphones, and any other devices if you
4 have not already done so. I would also like to
5 identify the FDA press contact, Tara Rabin. If you
6 are here, please stand.

7 My name is Mary Ellen McCann. I am the
8 acting chairperson of the Anesthetic and Analgesic
9 Drug Products Advisory Committee, and I will be
10 chairing this meeting. I will now call the meeting
11 of the Anesthetic and Analgesic Drug Products
12 Advisory Committee to order. We will start by
13 going around the table and introducing ourselves.
14 We will start with the FDA on my left and go around
15 the table.

16 DR. HERTZ: Good morning. I'm Sharon Hertz,
17 director for the Division of Anesthesia, Analgesia,
18 and Addiction Products.
19
20
21
22

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

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

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

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

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

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

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

22 DR. CHOI: Moon Hee Choi, designated federal

1 officer.

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

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

10 DR. HIGGINS: Jennifer Higgins, AADPAC
11 consumer representative.

12 DR. PORTER: Laura Porter, patient
13 representative.

14 DR. TERMAN: Greg Terman, professor of
15 anesthesiology and pain medicine at the University
16 of Washington in Seattle and director of the Acute
17 Pain Service at the University of Washington
18 Medical Center.

19 DR. ZACHAROFF: Good morning. Kevin
20 Zacharoff, anesthesiology and pain medicine,
21 faculty and clinical instructor at SUNY Stony Brook
22 School of Medicine.

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

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

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

18 In the spirit of the Federal Advisory
19 Committee Act and the Government in the Sunshine
20 Act, we ask that the advisory committee members
21 take care that their conversations about the topic
22 at hand take place in the open forum of the

1 meeting. We are aware that members of the media
2 are anxious to speak with the FDA about these
3 proceedings. However, FDA will refrain from
4 discussing the details of this meeting with the
5 media until its conclusion. Also, the committee is
6 reminded to please refrain from discussing the
7 meeting topic during breaks or lunch. Thank you.

8 Now, we now pass to Moon Hee Choi, who will
9 read the Conflict of Interest Statement.

10 **Conflict of Interest Statement**

11 DR. CHOI: The Food and Drug Administration
12 is convening today's meeting of the Anesthetic and
13 Analgesic Drug Products Advisory Committee under
14 the authority of the Federal Advisory Committee Act
15 of 1972. With the exception of the industry
16 representative, all members and temporary voting
17 members of the committee are special government
18 employees or regular federal employees from other
19 agencies and are subject to federal conflict of
20 interest laws and regulations.

21 The following information on the status of
22 this committee's compliance with federal ethics and

1 conflict of interest laws, covered by but not
2 limited to those found at 18 USC Section 208, is
3 being provided to participants in today's meeting
4 and to the public.

5 FDA has determined that members and
6 temporary voting members of this committee are in
7 compliance with federal ethics and conflict of
8 interest laws. Under 18 USC Section 208, Congress
9 has authorized FDA to grant waivers to special
10 government employees and regular federal employees
11 who have potential financial conflicts when it is
12 determined that the agency's need for a special
13 government employee's services outweighs his or her
14 potential financial conflict of interest or when
15 the interest of a regular federal employee is not
16 so substantial as to be deemed likely to affect the
17 integrity of the services which the government may
18 expect from the employee.

19 Related to the discussions of today's
20 meeting, members and temporary voting members of
21 this committee have been screened for potential
22 financial conflicts of interest of their own, as

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

8 Today's agenda involves discussion of
9 supplemental new drug application sNDA 022496/S-
10 009, for EXPAREL, bupivacaine liposome injectable
11 suspension, submitted by Pacira Pharmaceuticals to
12 produce local analgesia and as a nerve block to
13 produce regional analgesia. This is a particular
14 matters meeting during which specific matters
15 related to Pacira's sNDA will be discussed.

16 Based on the agenda for today's meeting and
17 all financial interests reported by the committee
18 members and temporary voting members, no conflict
19 of interest waivers have been issued in connection
20 with this meeting. To ensure transparency, we
21 encourage all standing committee members and
22 temporary voting members to disclose any public

1 statements that they have made concerning the
2 product at issue.

3 With respect to FDA's invited industry
4 representative, we would like to disclose that
5 Dr. Michele Hummel is participating in this meeting
6 as a nonvoting industry representative acting on
7 behalf of regulated industry. Dr. Hummel's role at
8 this meeting is to represent industry in general
9 and not any particular company.

10 We would like to remind members and
11 temporary voting members that if the discussions
12 involve any other products or firms not already on
13 the agenda for which an FDA participant has a
14 personal or imputed financial interest, the
15 participants need to exclude themselves from such
16 involvement, and their exclusion will be noted for
17 the record.

18 FDA encourages all other participants to
19 advise the committee of any financial relationships
20 that they may have with the firm at issue. Thank
21 you.

22 DR. McCANN: We will now proceed with the

1 FDA's introductory remarks from Dr. Sharon Hertz.

2 **FDA Introductory Remarks - Sharon Hertz**

3 DR. HERTZ: Good morning. Dr. McCann,
4 members of the AADPAC, invited guests, welcome. We
5 will continue our discussion of EXPAREL,
6 bupivacaine liposomal injection suspension today.
7 As I noted yesterday, because the applicant is
8 seeking to change the original indication as well
9 as add a new indication, data will be presented
10 from studies spanning the entire development
11 program.

12 As I mentioned yesterday, there are some
13 differences in opinion on how to interpret the
14 results of these studies. This morning you're
15 going to hear the presentations from FDA, then we
16 will have some additional discussion.

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

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

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

20 The use of local anesthetics as part of a
21 multimodal approach to postoperative pain
22 management has become more and more popular,

1 particularly as practitioners strive to reduce the
2 use of opioid analgesics. So as you consider the
3 efficacy data, we're also going to ask for your
4 thoughts about what constitutes a clinically
5 meaningful opioid-sparing effect across the data
6 that we will be presenting. We think it's
7 important because we think it's important for
8 prescribers to have a full understanding of the
9 effects of the new product and what the product is
10 capable of doing.

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

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

17 **FDA Presentation - Alla Bazini**

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

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

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

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

6 The initial EXPAREL NDA was approved in
7 2011. There were several studies submitted with
8 outcomes for infiltration. There were five phase 2
9 active control studies with bupivacaine; there were
10 three phase 3 active control studies with
11 bupivacaine; there were two phase 3
12 placebo-controlled studies with no active
13 comparator; and there was one phase 2 active
14 control study with outcomes for ankle block.

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

1 statistical difference in the study groups.

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

9 I'm highlighting study 210 because there was
10 some disagreement regarding the study results.

11 This was a phase 2 study comparing EXPAREL 133 and
12 266 milligrams to three-quarters percent
13 bupivacaine for breast augmentation. There were
14 two control groups that were matched for volume.
15 Because this was a phase 2 study, there were no
16 prespecified endpoints.

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

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

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

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

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

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

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

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

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

6 In the next several slides, I will present
7 more details regarding studies 322 and 323.

8 Study 322 evaluated the intercostal nerve block.
9 Subjects were randomized equally to EXPAREL 266 or
10 placebo, and there was no bupivacaine comparator
11 group. The study was mostly conducted in several
12 eastern European countries.

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

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

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

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

22 In the Integrated Summary of Efficacy, the

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

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

22 I will move on to discuss study 323 in the

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

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

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

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

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

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

1 details regarding these results shortly.

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

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

1 and motor deficits from the nerve block.

2 To address the deficiencies in the complete
3 response, the applicant resubmitted a supplement
4 NDA in 2017 with two new phase 3 studies.

5 Study 326 enrolled patients undergoing total knee
6 arthroplasty and administered a femoral nerve
7 block. Study 327 enrolled patients undergoing
8 total shoulder arthroplasty or a rotator cuff
9 repair and administered a brachial plexus block.
10 In addition, the applicant submitted two supportive
11 studies, 1601 and 1602, in the median and ulnar
12 nerve blocks, posterior tibial, and deep peroneal
13 nerve blocks, respectively.

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

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

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

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

16 Let's talk about the new studies. Study 326
17 was the femoral nerve study and TKA. Subjects were
18 randomized equally to EXPAREL 133, 266, or to
19 placebo. Although there wasn't a true active
20 comparator, all subjects did receive additional
21 40 milligrams of bupivacaine that was given via the
22 posterior capsule by the surgeons. You can see the

1 adjusted total bupivacaine doses here.

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

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

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

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

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

16 The final pivotal study I will discuss is
17 study 327 in the brachial plexus nerve block. The
18 subjects were originally randomized to EXPAREL 133,
19 266, or to placebo. Again, there were no
20 bupivacaine comparator groups. However, the
21 266-milligram cohort was continued after 15
22 subjects because interim PK data demonstrated

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

5 I would like to point out that the study
6 endpoints evaluated pain and opioid use for only
7 48 hours, whereas the other three pivotal studies
8 evaluated these endpoints for 72 hours. The study
9 results demonstrated a statistically significant
10 difference in all study endpoints at 48 hours.
11 Katherine Meaker will present data for these
12 endpoints for 72 hours in which the secondary
13 endpoint of opioid-free subjects becomes no longer
14 statistically significant.

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

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

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

3 **FDA Presentation - Katherine Meaker**

4 MS. MEAKER: Thank you, Dr. Bazini.

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

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

1 One study, the brachial plexus nerve study
2 327 was planned with 0 to 48 hours as the primary
3 efficacy time frame. The other three studies were
4 planned with 0 to 72 hours as the primary time
5 frame. For ease of discussion across the studies,
6 I will report the results for the 72-hour
7 postoperative period for all four studies. In
8 almost all results, the conclusions at 48 hours and
9 72 hours were consistent, which I will note during
10 my presentation.

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

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

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

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

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

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

4 I return now to the pain assessments for
5 each of the four nerve-block studies. I will show
6 mean pain at several time points across the 72-hour
7 time frame. Time is displayed on the horizontal
8 axis. Mean pain with 95 percent confidence
9 interval bars is shown on the vertical axis. As
10 shown here for the intercostal nerve-block study
11 322, the lines do not separate. This confirms the
12 conclusion from the analyses of the AUC pain that
13 there are no statistical differences in reduction
14 of pain between these treatment groups.

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

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

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

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

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

4 Returning to the brachial plexus nerve study
5 327, the lines clearly separate confirming the
6 analyses of the AUC pain endpoint. Note that the
7 primary endpoint was defined at 0 to 48 hours and
8 showed a statistical difference between the groups
9 in AUC pain. This separation observed through 48
10 hours extended through 72 hours.

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

22 The outcomes we considered to assess opioid

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

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

14 As in analyses of the pain outcome, the same
15 two studies showed a statistically significant
16 difference in the amount of total opioid
17 consumption over the 72-hour time frame. In the
18 brachial plexus nerve-block study, the EXPAREL
19 133-milligram group used an average of
20 97 milligrams less opioid rescue than placebo
21 group. In the femoral nerve-block study without
22 bupivacaine posterior capsule injection, the

1 EXPAREL 266-milligram group used an average of
2 27 milligrams less opioid rescue than the placebo
3 group. Dr. Bazini will discuss the clinical
4 relevance of these reductions in opioid use.

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

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

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

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

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

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

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

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

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

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

7 This slide presents the conclusions from the
8 statistical analyses of the pain and opioid use
9 endpoints through 72 hours post-op. As previously
10 mentioned in studies 327 and 323, treatment with
11 EXPAREL when compared to placebo demonstrated a
12 statistically significant reduction in
13 postoperative pain and total amount of post-
14 surgical opioid use through 72 hours. In study
15 327, treatment with EXPAREL also demonstrated a
16 significant difference in the time to first use of
17 opioids compared to placebo. In all four studies,
18 most if not all patients used opioids by 72 hours
19 post-op.

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

FDA Presentation - Alla Bazini

1
2 DR. BAZINI: Although you have already seen
3 the results for the first femoral nerve-block
4 study, study 323, I would like to reiterate that
5 statistically this study did meet its primary
6 efficacy endpoint as well as the secondary efficacy
7 endpoint of total opioid use in 72 hours. However,
8 as you just saw, the actual pain score differences
9 between the two study groups were only around 1 to
10 2 points across the entire 72 hours. This amount
11 of difference is unlikely to have meaningful
12 clinical impact on clinical outcomes. In addition,
13 no subject remained opioid free and total opioid
14 consumption was still considerable in the EXPAREL
15 arms.

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

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

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

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

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

4 In addition, similar baseline patient
5 characteristics were described in study 327 where
6 25 percent of the study population were enrolled in
7 the same European study centers or study 326. And
8 again, as we saw, that study did meet its
9 statistical significance.

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

22 Kate Meaker had already discussed the

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

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

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

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

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

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

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

1 control failed to demonstrate clinical or
2 statistical difference between EXPAREL and
3 bupivacaine. Therefore, based on the data
4 available, EXPAREL administered via femoral nerve
5 block appears to have no advantage over bupivacaine
6 administered via posterior capsule in the first
7 72 hours after total knee arthroplasty. In
8 addition, no opioid-sparing effect was
9 demonstrated.

10 Unlike study 326, study 327 met statistical
11 significance on all primary and secondary endpoints
12 in the first 48 hours. There were no major
13 differences in efficacy between study regions or in
14 the patient subpopulations. In the first 48 hours,
15 9 subjects in the EXPAREL remained opioid free and
16 one subject in the placebo arm.

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

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

4 I will now briefly discuss the supportive
5 studies submitted by the applicant. Study 1601
6 compared the admixture of EXPAREL plus bupivacaine,
7 first as bupivacaine alone in subjects getting
8 median and ulnar nerve blocks for Dupuytren's
9 contracture release. It should be noted that this
10 study, as well as study 1602, which I will discuss
11 next, were conducted in Belgium, and the PI and
12 sub-investigators of the study were the same
13 investigators as the Belgian sites in study 326 and
14 327.

15 Although the total volume of the injected is
16 15 mL in each study group, you will notice that the
17 EXPAREL-bupivacaine group received more than double
18 the total milligrams of bupivacaine with the
19 regular bupivacaine group getting 75 milligrams
20 total and the bupivacaine-EXPAREL group getting
21 155 milligrams total. There were several efficacy
22 endpoints evaluated, and multiple assessments were

1 performed through day 7.

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

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

22 Study 1602 also compared an admixture of

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

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

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

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

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

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

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

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

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

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

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

15 To summarize the efficacy section of my
16 talk, at this time we have two pivotal studies that
17 did not meet their primary efficacy endpoint of AUC
18 of pain intensity scores in the first
19 72 postoperative hours. Study 322 in the
20 intercostal nerve block likely failed due to
21 administration of EXPAREL into a highly vascular
22 compartment, which possibly led to rapid absorption

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

7 We also have two pivotal studies that met
8 their primary efficacy endpoints. Although study
9 323, which was the first femoral nerve-block study,
10 demonstrated statistical significance in the AUC of
11 pain intensity scores in the first 72 hours, as I
12 previously discussed, the overall differences in
13 pain scores were approximately 1 to 2 points, which
14 questions the clinical relevance of this data. In
15 addition, the study did not adequately characterize
16 the safety profile of EXPAREL via femoral nerve
17 block due to its truncated monitoring period and
18 incomplete safety assessments.

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

1 pivotal studies were able to demonstrate
2 significantly meaningful opioid sparing since
3 almost all subjects in all studies still require
4 significant amount of opioids in the first
5 72 hours.

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

12 **FDA Presentation - Suresh Naraharisetti**

13 DR. NARAHARISETTI: Thank you, Dr. Bazini.

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

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

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

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

22 EXPAREL was approved for surgical procedures

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

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

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

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

4 Say for example, at 12 hour after EXPAREL
5 administration the individual concentrations in
6 patients ranged between 47 nanogram per mL to
7 1210 nanogram per mL. Similar scatter can be
8 observed at later points till 60 hours. The
9 bottom-left figure represents mean systemic PK
10 profile of EXPAREL 106 milligram in bunionectomy.
11 The scatter of individual concentrations is plotted
12 on the bottom right figure. Overall, these two
13 infiltration procedures show that the systemic
14 absorption of bupivacaine from EXPAREL between the
15 individuals is variable.

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

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

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

14 The bupivacaine from EXPAREL liposomes is
15 released over a period of time. To compare the
16 systemic exposure of bupivacaine from EXPAREL and
17 bupivacaine in a known infiltration procedure,
18 inguinal-hernia repair study was utilized. The
19 study was a phase 2, double-blind, dose-escalation
20 safety, efficacy, and PK study in which escalating
21 single doses of EXPAREL were compared with a single
22 100-milligram dose of bupivacaine. Both studies

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

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

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

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

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

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

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

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

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

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

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

4 As you heard from earlier presentations, it
5 is noted that an additional 40-milligram
6 bupivacaine was administered in the posterior
7 capsule in all treatment groups before closure of
8 prosthesis, so for EXPAREL 266-milligram treatment
9 group, the total dose of bupivacaine becomes
10 306 milligram. In study 327, EXPAREL was
11 administered using ultrasound guidance. Although
12 PK was evaluated at different doses of EXPAREL, for
13 comparison purposes, I will only discuss the PK
14 findings from the highest dose, 266 milligram.

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

1 represent the brachial plexus nerve block.

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

9 Usually from the mean systemic profiles in
10 the femoral nerve-block studies, the time to
11 maximum concentrations for EXPAREL appears beyond
12 80 hours. The individual Tmax frequency
13 distribution is presented in the following slides.
14 Overall, for the same dose, the systemic PK
15 profiles of EXPAREL are different between
16 procedures.

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

1 in individual subjects. For example, in study 326
2 shown on the top right at 108 hours, which is equal
3 to 4.5 days after surgery, the individual
4 concentrations of EXPAREL vary between 43 nanogram
5 per mL to 1120 nanogram per mL. A similar scatter
6 was observed at several time points once after drug
7 administration. Several concentrations are beyond
8 1000 nanogram per mL in the study.

9 In the intercostal nerve block, which showed
10 instantaneous absorption shown in the bottom left,
11 similar scatter was observed till last time point
12 of sample collection that is 72 hours. The maximum
13 concentration observed in this study is
14 2090 nanogram per mL.

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

22 Knudsen and co-workers state that the mean

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

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

10 This figure shows the individual Tmax
11 distribution in nerve-block studies. First, I will
12 focus on femoral nerve-block studies. The Tmax of
13 EXPAREL in femoral nerve-block studies is much
14 delayed. Study 323 is shown in black horizontal
15 bars and study 326 is in black solid bars. The
16 median Tmax in study 323 is 80 hours with a range
17 of 60 to 96 hours. The median Tmax in study 326 is
18 72 hours with a much wider range of 2.5 to
19 108 hours observed in different patients.

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

1 to 48 hours. The brachial plexus nerve block shown
2 in bars with black dots, the median Tmax is
3 48 hours with a range of 24 to 72 hours. Overall,
4 the time to peak concentrations of EXPAREL varies
5 widely with a range of 0.5 to 108 hours requiring a
6 wide range of safety monitoring for bupivacaine
7 between different nerve-block procedures.

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

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

22 Now I'll focus on all four studies.

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

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

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

10 Number 3, there was 50 percent difference in
11 dose normalized AUC between study 326 and study
12 327. There was 70 percent difference in Cmax
13 between study 322 and study 327 for the same
14 266-milligram dose.

15 Now, to compare the systemic exposure
16 between EXPAREL and bupivacaine in the nerve-block
17 setting, the ankle block study for bunionectomy was
18 utilized. The study was a phase 2 efficacy,
19 safety, and PK study in which single escalating
20 doses of EXPAREL were compared to single
21 125-milligram dose of bupivacaine. Study drugs
22 were administered via ankle block. PK was compared

1 between EXPAREL 155 milligram and bupivacaine 125
2 milligram.

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

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

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

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

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

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

22 **FDA Presentation - Alla Bazini**

1 DR. BAZINI: Thank you, Dr. Naraharisetti.

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

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

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

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

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

19 In the next several slides, I will discuss
20 how the applicant addressed these deficiencies. In
21 2017, the applicant resubmitted reanalyzed Holter
22 monitor data through 72 hours and ECG data from

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

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

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

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

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

14 There were several subjects who had
15 persistent sensory deficits at 120 hours in study
16 326, the second femoral nerve-block study. The
17 number of subjects with persistent sensory deficits
18 increased from placebo group to the EXPAREL 133-
19 milligram group and further increased to the
20 EXPAREL 266-milligram group.

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

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

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

14 This table summarizes time to loss of motor
15 function in the same study. It should be noted
16 that subjects at the Belgian site, which had
17 50 percent of the study population, were
18 immobilized for the first 2 to 3 postoperative
19 days, which is a common surgical practice at this
20 site. Due to this immobilization, no motor
21 assessments were performed in these subjects.
22 Since the data for onset of motor loss from about

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

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

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

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

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

5 Although it is possible that either
6 generalized postoperative motor weakness or the
7 femoral nerve block itself may have contributed to
8 this increased incidence of falls in the treatment
9 groups, in the absence of an active control arm
10 with bupivacaine administered in the same manner it
11 is impossible to make such a conclusion.

12 Therefore, at this time, we must conclude that
13 EXPAREL may lead to increased incidence of falls.

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

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

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

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

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

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

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

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

4 The FAERS search included six years for
5 EXPAREL since it was approved in October 2011. The
6 FAERS search for the non-extended release local
7 anesthetics included the past 11 years in an effort
8 to retrieve the most up to date prescribing
9 practices. Of note, DPV defined rapid onset of
10 LAST as occurring less than an hour and delayed
11 onset LAST as occurring greater than an hour to
12 96 hours.

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

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

1 bottom dotted line. If you look at the bupivacaine
2 products combined, there were approximately
3 20 million eaches sold with EXPAREL sales equaling
4 less than 1 million or 4 percent of the bupivacaine
5 sales.

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

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

1 amongst the products.

2 There were a total of 111 cases of LAST with
3 39 attributed to EXPAREL versus 72 attributed to
4 other local anesthetics. The number of cases of
5 rapid onset of LAST and delayed LAST was similar
6 with EXPAREL, whereas most cases of LAST with other
7 local anesthetics were rapid in onset. There was
8 also a total of 8 fatalities, 5 of which were
9 attributed to EXPAREL. Clinical manifestations
10 involve signs and symptoms of cardiovascular or
11 central nervous system toxicity, and lipid emulsion
12 was used in some instances for treatment.

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

21 In a review of published cases of LAST from
22 1979 to 2009, Di Gregorio and colleagues wrote, and

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

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

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

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

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

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

22 This concludes my presentation this morning.

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

3 **Clarifying Questions**

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

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

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

15 DR. HIGGINS: Thank you.

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

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

1 66-year-old male; and an 87-year-old female. There
2 was one case that didn't report the age.

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

5 MS. CASCIO: Yes. For EXPAREL, it was the
6 60 year old; the 50 year old; 66 year old; and 87
7 year old.

8 DR. HIGGINS: Thank you.

9 MS. CASCIO: Sure.

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

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

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

1 DR. McCANN: Dr. Craig?

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

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

18 DR. McCANN: Dr. Litman?

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

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

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

8 DR. LITMAN: Sure. Thanks.

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

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

19 DR. McCANN: Dr. Porter?

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

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

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

8 DR. PORTER: So they're additional then.

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

12 DR. PORTER: Okay. Thank you.

13 DR. McCANN: Dr. Zacharoff?

14 DR. ZACHAROFF: Kevin Zacharoff.

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

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

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

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

8 (No response.)

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

12 DR. McCANN: Dr. Galinkin?

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

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

21 DR. GALINKIN: Or does the company?

22 DR. HERTZ: General data?

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

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

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

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

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

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

12 DR. HERTZ: Purely for safety.

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

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

1 of those?

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

5 DR. McCANN: Dr. Terman?

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

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

17 DR. TERMAN: Great.

18 MS. MEAKER: Okay.

19 DR. TERMAN: The second question I have --

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

22 DR. TERMAN: Sure.

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

7 DR. TERMAN: Right. So --

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

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

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

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

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

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

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

8 What sorts of data is requested there?

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

1 DR. TERMAN: Okay.

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

5 DR. TERMAN: Okay.

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

7 Dr. Porter?

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

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

15 DR. PORTER: Okay.

16 DR. McCANN: Dr. Zacharoff?

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

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

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

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

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

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

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

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

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

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

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

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

1 define what it is.

2 DR. McCANN: Dr. Gulur?

3 DR. GULUR: Thank you, Dr. McCann.

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

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

16 DR. GULUR: Thank you.

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

20 (No response.)

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

1 clarifying slides?

2 DR. HERTZ: Yes.

3 DR. McCANN: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 DR. HERTZ: Again, we don't know that
2 EXPAREL lasts for 72 hours independent of
3 bupivacaine. We have outcome data for AUC for
4 72 hours, but that's not necessarily what we find
5 in the pain curves. So these are the problems with
6 the placebo-controlled studies, and we don't yet
7 know for a fact that there is an added duration
8 effect. That's the point.

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

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

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

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

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

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

1 trying to make the point that even bupivacaine
2 fails?

3 DR. SCRANTON: Yes, sir?

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

7 DR. SCRANTON: This was the publication
8 here. In general, if you look even across all pain
9 trials for pain studies, the success is around
10 50 percent. I'm sorry. Here it is.

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

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

22 DR. LITMAN: I agree, but that slide

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

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

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

1 comparable with EXPAREL

2 DR. SCRANTON: Thank you.

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

12 DR. LITMAN: Okay.

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

19 DR. LITMAN: Thank you.

20 DR. CONNER: Thank you.

21 DR. McCANN: Dr. Terman?

22 DR. TERMAN: Thank you. Greg Terman. The

1 9 milligrams that you gave, what kind of volume is
2 that? I apologize for not knowing that.

3 DR. SCRANTON: This was the dose for giving
4 a dose -- we had to change the concentration based
5 on the milligrams per mL here on the right, dose
6 concentration milligram per mL, to achieve an
7 equivalent dose level over milligram per kilogram.
8 So if I were to extrapolate, for example,
9 4.5 milligram per kilogram, that would approximate,
10 in a 60-kilogram adult, a full dose of our vial of
11 EXPAREL, 266 milligrams.

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

14 DR. SCRANTON: So if this was 7 --

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

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

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

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

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

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

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

13 DR. BYRAM: Good morning. My name is
14 Susanna Byram. I'm an assistant professor at
15 Loyola University in anesthesia and critical care
16 medicine. Also, I'm a basic scientist, and I do
17 nerve injury and repair research for the last
18 20 years as a basic scientist in animal models. In
19 my experience using EXPAREL in my lab, as well as
20 just the review of some other laboratories that
21 have looked at EXPAREL in preclinical models,
22 there's been no evidence of toxicity to nerves.

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

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

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

22 DR. McCANN: Dr. Gulur?

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

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

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

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

21 DR. GULUR: Thank you.

22 DR. McCANN: Are there any more questions?

1 (No response.)

2 DR. McCANN: If not, we'll break for
3 20 minutes, which will take us to 10:36. Just to
4 remind you, there will be no discussion of the
5 meeting topic during the break amongst yourselves
6 or with any member of the audience. Thank you.

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

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

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

22 In response to the question about the

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

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

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

20 DR. BAZINI: 266.

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

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

4 DR. CONNER: This is Jason Conner. Yes.
5 Dr. Terman, you asked about the non-imputed data
6 for 327 in particular. If we can go to the core
7 slide. This is it, core slide 36. I'm just going
8 to start by showing you the raw. This was the raw
9 data, so you can see how the curves go down.
10 Slide PE-14, here you can see how they go down.
11 This is just the raw data. You can see scores went
12 from, on average, a pain score difference of about
13 2.5 to 88 divided by 48 is a pain score difference
14 of about 1.8.

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

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

3 DR. McCANN: Any further questions for the
4 FDA?

5 (No response.)

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

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

13 Are there any questions for the applicant?

14 DR. McCANN: Dr. Terman?

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

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

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

7 DR. McCANN: Dr. Gulur?

8 DR. GULUR: Thank you, Dr. McCann.

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

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

1 that case, they're doing the cases simultaneously,
2 two different teams, and they're doing a local
3 infiltration of EXPAREL at the full dose,
4 266 milligrams in each knee, so double our
5 recommended dose. And they were also doing
6 co-administration of 150 milligrams total dose
7 bupivacaine 75 per knee.

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

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

1 DR. McCANN: Dr. Xu?

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

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

8 DR. XU: It should be micrograms.

9 DR. SCRANTON: Yes, sir.

10 DR. XU: Okay.

11 DR. SCRANTON: Thank you.

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

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

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

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

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

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

12 DR. GULUR: In the upper extremity?

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

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

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

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

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

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

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

6 DR. SCRANTON: From a continuous nerve
7 block?

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

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

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

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

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

9 DR. GULUR: You do not recommend?

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

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

16 DR. SCRANTON: Yes, exactly. Thank you.

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

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

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

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

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

1 blocks for cardiac surgical procedures and many
2 thoracotomies.

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

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

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

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

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

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

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

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

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

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

9 DR. SCRANTON: Sure. Here's how our current
10 label reads to address that issue. Commonly for
11 bupivacaine, the total dose per the label is a
12 maximum dose of 400 milligrams and 24 for
13 immediate-release bupivacaine. So here our dose is
14 266 milligram, and not to exceed that dose. I'm
15 not aware of a package insert for IV lidocaine.

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

1 maximum that should be given.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 DR. SCRANTON: For repeat exposure for
7 EXPAREL --

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

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

12 DR. WINSTON: Hi. Roy Winston, Pacira
13 Pharmaceuticals. Actually in the label, right now
14 currently -- and this is not planned on
15 changing -- it does say in the first 96 hours after
16 administration of EXPAREL, no other local
17 anesthetics should be administered during that
18 96 hours.

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

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

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

11 DR. WINSTON: During the first

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

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

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

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

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

9 DR. GULUR: Thank you.

10 DR. SCRANTON: Thank you.

11 DR. McCANN: Dr. Litman?

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

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

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

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

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

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

10 DR. SCRANTON: Thank you.

11 DR. McCANN: Dr. Zacharoff?

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

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

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

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

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

15 We started that out to 20 minutes and being
16 pretty conservative that if you separate in time
17 from that, it has no impact on the release of our
18 drug. So if you're going to give lidocaine, wait
19 20 minutes, then give EXPAREL, that wouldn't have
20 any impact. Also, if you're giving lidocaine at
21 some other site, you're putting in an IV and need a
22 little lidocaine, that wouldn't have any impact on

1 our drug whatsoever.

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

4 DR. SCRANTON: Correct.

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

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

1 was no impact on the release characteristics of our
2 DepoFoam.

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

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

11 DR. ZACHAROFF: Thank you.

12 DR. McCANN: Dr. Gulur?

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

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

3 DR. SCRANTON: Go ahead.

4 DR. WINSTON: Right. To take those one at a
5 time, I think for the admixing, that's up to
6 50 percent of the dose. So with the 266-milligram
7 initial dose, you can do half again with plain
8 bupivacaine. And then after that's administered,
9 we recommend no other local anesthetics for
10 96 hours.

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

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

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

22 DR. WINSTON: At the same site.

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

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

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

17 DR. WINSTON: But again, your starting dose,
18 you wouldn't want to exceed the recommended
19 50 percent totally anywhere in the body at that
20 point. And I think really, from a safety concern,
21 we know that the PK cumulatively from the EXPAREL
22 and from that added 50 percent of bupivacaine won't

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

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

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

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

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

22 DR. GULUR: And without confounding the

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

5 DR. SCRANTON: Do not.

6 DR. GULUR: -- do not.

7 DR. SCRANTON: Correct.

8 DR. GULUR: Okay. Thank you very much.

9 DR. McCANN: Dr. Galinkin?

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

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

19 DR. HERTZ: Efficacy and safety.

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

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

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

9 DR. McCANN: Are there any more questions?

10 (No response.)

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

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

21

22

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

1 (12:30 p.m.)

2 **Open Public Hearing**

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

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

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

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

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

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

22 DR. HAVARD: Thanks to the committee for

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

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

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

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

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

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

1 surrounding areas of the surgical site. The
2 patient is discharged home with a combination of
3 NSAIDs and acetaminophen for a period of 5 to
4 7 days. Postoperative visits related to negative
5 side effects have been decreased significantly.

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

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

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

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

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

12 We followed the study protocol very strictly
13 because I really wanted to see if it's what they
14 say it is. I was there to observe my patients day
15 and night, and I did the mini main [indiscernible]
16 block first-handed and did the main physical exam
17 myself, even at midnight to 2:00 in the morning.
18 The reason I found I was actually pleasantly
19 surprised or not surprised is that many of my study
20 patients, they do have prolonged nerve block, and
21 some of them have the sensory deficit up to
22 5.7 days, which is not surprising to some, but it

1 was a pleasant surprise to me.

2 The other phenomena I want to emphasize was
3 what I observed about the smooth recovery of my
4 patients after the shoulder and the knee surgeries.
5 In orthopedic literature, there's a well described
6 phenomenon called the rebounding pain, which means
7 when block is gone, your pain is back, and the pain
8 is severe, and the patient frequently requires
9 escalating dose of narcotics. In fact, in many
10 studies, we note for single-shot interscalene
11 block, it lasts about 6 to 8 days, and the patients
12 will have more pain when block is gone. At a
13 24-hour time point, they actually require more
14 narcotics compared to a patient without
15 interscalene block. So patients will often
16 describe that my pain continues day and night.
17 When block is gone, it's really, really bad.

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

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

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

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

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

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

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

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

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

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

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

1 of those examples. Please consider this. Thank
2 you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. SESSLER: Good afternoon. I'm Dan

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

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

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

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

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

13 Encapsulated bupivacaine is a distinct
14 advantage because it lasts for days. This gets
15 patients through the very acute, several days of
16 sharp surgical pain. Thereafter, it's almost
17 always possible to transition patients directly
18 into a non-opioid alternative. Because of its
19 obvious duration benefit, encapsulated bupivacaine
20 is frequently used in pediatric patients off label.
21 For example, at the Cleveland Clinic, we identified
22 500 pediatric patients who had encapsulated

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 I firmly believe that the use of this nerve
13 block can minimize exposure to opioids, therefore
14 it will significantly prevent potential risk of
15 addiction to patients having surgery. If
16 physicians reduced the number of opioid
17 prescriptions written each year by just 10 percent,
18 it would result in 300,000 fewer patients becoming
19 persistent opiate users following their surgery;
20 300,000 per year, almost a billion dollars,
21 \$830 million a year in lower drug costs.

22 As you know, deaths from drug overdose have

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

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

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

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

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

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

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

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

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

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

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

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

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

1 no conflicts of interest.

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

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

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

1 demonstrated efficacy in one instance was due to
2 chance.

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

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

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

1 should be clearly marked as a contraindication on
2 the label.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 travel.

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

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

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

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

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

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

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

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

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

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

1 prescription drugs except an occasional one for an
2 irritable bowel.

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

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

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

22 DR. McCANN: Will speaker number 14 step up

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

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

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

1 period until functional recovery is achieved.

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

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

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

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

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

22 DR. McCANN: Will speaker number 15 step up

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

4 (No response.)

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

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

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

1 its efficacy. I have two brief messages.

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

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

22 The proposed mechanisms for these outcomes

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

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

22 DR. McCANN: If speaker 15 is here, would

1 they please step up to the podium?

2 (No response.)

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

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

12 **Charge to the Committee - Sharon Hertz**

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

1 proposed indication.

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

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

16 **Questions to the Committee and Discussion**

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

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

9 (No response.)

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

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

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

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

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

8 DR. McCANN: Dr. Gulur?

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

17 DR. McCANN: Dr. Galinkin?

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

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

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

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

14 Does that help guide the response a little?

15 (No response.)

16 DR. HERTZ: Apparently not.

17 DR. McCANN: Dr. Litman?

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

1 judgment, essentially, in the end.

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

12 DR. McCANN: Dr. Zacharoff?

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

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

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

15 DR. McCANN: Dr. Gulur?

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

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

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

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

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

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

4 DR. McCANN: Dr. Terman?

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

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

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

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

6 (No response.)

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

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

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

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

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

16 Dr. Galinkin?

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

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

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

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

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

1 my biggest concerns with this medication.

2 DR. McCANN: Dr. Craig?

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

13 DR. McCANN: Dr. Porter?

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

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

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

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

10 DR. McCANN: Dr. Zacharoff?

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

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

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

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

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

22 DR. McCANN: Any other comments? Dr.

1 Shoben?

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

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

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

1 contradictions.

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

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

1 everybody if possible.

2 Dr. Craig?

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

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

12 DR. CRAIG: Correct.

13 DR. McCANN: -- individual nerve block.

14 DR. CRAIG: Correct.

15 DR. McCANN: Dr. Litman?

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

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

22 DR. LITMAN: So even a nerve block --

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

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

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

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

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

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

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

9 (Laughter.)

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

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

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

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

14 DR. McCANN: Dr. Terman?

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

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

3 DR. McCANN: Dr. Zacharoff?

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

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

21 DR. McCANN: Any other comments?

22 (No response.)

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

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

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

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

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

4 DR. McCANN: Dr. Terman?

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

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

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

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

8 DR. McCANN: Dr. Litman?

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

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

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

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

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

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

22 DR. McCANN: Dr. Gulur?

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

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

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

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

14 DR. McCANN: Dr. Galinkin?

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

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

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

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

1 in my opinion.

2 DR. McCANN: Dr. Zacharoff?

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

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

1 much else as we could.

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

16 DR. McCANN: Dr. Shoben?

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

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

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

17 DR. McCANN: Any other comments?

18 (No response.)

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

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

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

16 Dr. Zacharoff?

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

20 DR. McCANN: Absolutely. Sorry.

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

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

4 Dr. Litman?

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

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

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

18 Dr. Litman?

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

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

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

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

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

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

16 DR. McCANN: Dr. Shoben?

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

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

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

12 DR. McCANN: Dr. Zacharoff?

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

22 DR. HERTZ: I think we meant it as

1 demonstrating the safety of the product.

2 DR. ZACHAROFF: Okay.

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

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

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

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

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

14 DR. McCANN: Dr. Higgins?

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

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

6 DR. McCANN: Dr. Porter?

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

15 DR. McCANN: Dr. Galinkin?

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

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

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

14 DR. McCANN: Dr. Terman?

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

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

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

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

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

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

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

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

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

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

10 DR. McCANN: Dr. Gulur?

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

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

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

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

15 DR. McCANN: Any other comments?

16 (No response.)

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

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

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

22 DR. GALINKIN: I just want to point out from

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

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

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

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

19 DR. McCANN: Dr. Zacharoff?

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

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

7 DR. McCANN: Dr. Craig?

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

21 DR. McCANN: Dr. Galinkin?

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

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

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

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

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

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

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

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

11 DR. McCANN: Any other comments?

12 (No response.)

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

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

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

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

10 DR. McCANN: Dr. Higgins?

11 DR. HIGGINS: Very succinctly, I would say
12 yes. I feel like more studies are needed before
13 approval.

14 DR. McCANN: Dr. Zacharoff?

15 DR. ZACHAROFF: If I look at this question,
16 I think if I were an opioid, what discussion would
17 be having. And the answer we'd be saying is yes,
18 we need additional studies in order to support this
19 supplemental NDA that demonstrate efficacy, that
20 demonstrate the issues of safety and so on and so
21 forth. Those are my outstanding issues, and if we
22 choose not to let the non-opioid quality cloud our

1 judgment, then the answer has to be yes in my mind.

2 DR. McCANN: Dr. Terman?

3 DR. TERMAN: I am a big fan of local
4 anesthetics, and if EXPAREL can get people who
5 haven't been using local anesthetics to use local
6 anesthetics, that's wonderful. I'm all in favor.
7 But one of the things that concerns me the most,
8 and this hits home to my practice, is what I talked
9 about before, that when you use EXPAREL, it ties my
10 hands for using other local anesthetics for several
11 days and turns me into a non-opiate sparer but an
12 opiate purveyor because all I
13 have -- really, high-efficacy analgesics is up and
14 up on the opiates, and that is a risk in a way.
15 That is a problem with not comparing the true local
16 anesthetic comparator because if you use
17 one -- it's not like giving gabapentin and then I
18 can always give something else if that's not
19 sufficient. This is something that if I give and
20 it doesn't work, I'm out of luck. I've got to go
21 to something completely different, and
22 unfortunately, completely different is just the

1 opposite of what we heard today from the public.
2 So this is a really important issue for me,
3 personally.

4 In terms of supplementing the NDA, obviously
5 additional studies as has been said, although I do
6 think the efficacy has apparently been
7 demonstrated, at least in some blocks. The
8 comparator with the active comparison is really
9 important to figure out where this drug positions
10 itself in the landscape.

11 DR. McCANN: By more studies, you mean
12 pre-approval or post-approval?

13 DR. TERMAN: Well, in the last question, we
14 didn't talk about the specific indication for nerve
15 blocks. I'm not sure that it says that in this
16 question either, but I would say that need to be
17 done. Whether it's pre-approval or post-approval
18 is less important to me.

19 DR. McCANN: Dr. Shoben?

20 DR. SHO BEN: I think the outstanding issue
21 for me -- and it's been hit on a couple different
22 times, but I just wanted to make the point myself,

1 that this issue of marketing in a possible
2 opioid-sparing medication, you absolutely need the
3 longitudinal data to show that they're off opioids
4 sooner, that there's less addiction, there's less
5 long-term use. There's that sort of thing. And I
6 would be fine with that coming post-approval. I
7 just want that to be clear that you can't possibly
8 approve this opioid sparing and sell it as such
9 just based on the differences that we've seen in
10 the clinical trials.

11 DR. McCANN: Dr. Porter?

12 DR. PORTER: I think definitely more studies
13 need to be done, but I'm not sure that the issue
14 today is about opioid sparing. They're asking for
15 the supplemental NDA to just change what we've
16 already read. I don't think they're asking for it
17 to say opioid sparing. I think that's a different
18 issue. But I think that more studies need to be
19 done, and I'm okay with either post- or
20 pre-approval.

21 DR. McCANN: Dr. Craig?

22 DR. CRAIG: In regards to this sNA, I don't

1 think we need more studies in my opinion. I think
2 that there's enough studies to help guide this
3 decision because then I would challenge the people
4 who say that we need more studies what kind of
5 studies do we need. The active comparator studies
6 would be nice. And if you look at most of the
7 active comparator studies, there's no difference
8 between EXPAREL and active comparator in the
9 regular release bupivacaine.

10 That's a specific issue that clinicians can
11 help to digest and to understand whether they need
12 to use it in their practice or not. That's not
13 really the question. The questions is do we need
14 more data to support this expanded indication. My
15 opinion, no.

16 DR. McCANN: Are there any other comments?

17 (No response.)

18 DR. McCANN: Summarize. Most people felt
19 more studies were needed. Some people felt it
20 should be done pre-approval; others thought
21 post-approval especially for the indication for
22 opioid sparing. The concern was brought up that's

1 a little bit tangential, that one of the issues
2 with failed EXPAREL block is that it turns the
3 physician into an opioid purveyor. That concern
4 could maybe be mitigated by doing active comparator
5 studies, which would demonstrate whether you were
6 purveying more or less with EXPAREL.

7 I think we're getting ready for the voting
8 stage. If there are no further discussions on this
9 question, we will begin the voting process. We
10 will be using an electronic voting system for this
11 meeting. Once we begin the vote, the buttons will
12 start flashing and will continue to flash even
13 after you've entered your vote. Please press the
14 button firmly that corresponds to your vote. If
15 you are unsure of your vote or you wish to change
16 your vote, you may press the corresponding button
17 until the vote is closed.

18 After everyone has completed the vote, the
19 vote will be locked in. The vote will then be
20 displayed on the screen. The DFO will read the
21 vote from the screen into the record. Next we will
22 go around the room, and each individual who voted

1 will state their name and vote into the record.
2 You can also state the reason why you voted as you
3 did if you want to. We will continue in the same
4 manner until all questions have been answered or
5 discussed.

6 The question for all of us is, do the
7 efficacy, safety, and overall risk-benefit profile
8 of EXPAREL support the approval of the supplemental
9 application to add an indication for nerve block to
10 produce regional anesthesia or any individual
11 nerve-block indications?

12 Are there any questions about the question?
13 Dr. Craig?

14 DR. CRAIG: I hate to ask, but could we just
15 modify the question a bit to include the language
16 Dr. Zacharoff proposed? I think as written, I'd
17 say no, but if it could be modified and tweaked a
18 bit, then I think the answer changes to yes.

19 DR. HERTZ: So we're trying to get here
20 about the nerve-block piece rather than the first
21 part piece. Does that help? It doesn't look like
22 it. The way one could rephrase this is do the data

1 submitted in support of the request for a nerve-
2 block indication support adding that on to the
3 indication as an additional indication.

4 DR. CRAIG: Okay.

5 DR. HIGGINS: Forgive me. I didn't follow
6 that. Could that be repeated, maybe stated more
7 declaratively?

8 DR. HERTZ: What we're trying to ask for the
9 vote is -- time out.

10 (Pause.)

11 DR. HERTZ: I'm just going to fill a little
12 space while they take care of posting that.

13 It's really been interesting to hear the
14 response to our questions, and I think what it
15 reflects is the difference between being immersed
16 in something and coming in and trying to understand
17 it when you're not immersed in it; because we
18 really think these questions are so crystal clear
19 when we write them, and you frequently school us
20 that it's not the case.

21 (Pause.)

22 DR. McCANN: It's a much shorter question.

1 That's great. Do the data submitted support
2 approval of an additional indication for nerve
3 block?

4 Dr. Zacharoff?

5 DR. ZACHAROFF: I would think the word
6 "postoperative" would need to be in there.

7 DR. McCANN: What would you suggest,
8 Dr. Zacharoff?

9 DR. ZACHAROFF: It's an additional
10 indication for nerve-block use for bupivacaine
11 analgesia. I'm just trying to clarify.

12 DR. HERTZ: Yes.

13 DR. McCANN: So is everybody ready to vote?
14 Let's vote.

15 Everybody has voted. The vote is now
16 complete.

17 (Pause.)

18 DR. McCANN: Somebody had an emergency
19 bathroom break.

20 (Pause.)

21 DR. HERTZ: We're going to take a -- we'll
22 go with a five-minute break just to kind -- just

1 make sure everyone's back because then we can
2 actually take the vote, and do one more round, and
3 let you all --

4 (Laughter.)

5 DR. HERTZ: Did we lose anyone from the
6 table? Never mind; no break. Skip the break.

7 (Voting.)

8 DR. McCANN: Now that the vote is complete,
9 we will go around the table and have everyone who
10 voted state their name, vote, and if you want to,
11 you can state the reason why you voted as you did
12 into the record. We'll start with Dr. Shoben.

13 DR. SHO BEN: Abby Shoben. I voted no for
14 most of the reasons I've already said. I don't
15 think the efficacy data are there. Yes, the
16 brachial plexus data looks promising, but given the
17 amount of variability in the other studies and the
18 amount of variability in the PK data, I'm not
19 convinced of the efficacy. And in addition there are
20 some safety concerns that I would like to see more
21 data on before approval.

22 DR. CRAIG: Dave Craig. I voted yes, I

1 think primarily because of how I stated before. I
2 think that the data is there for at least two of
3 the areas of block based on the studies that were
4 submitted, so that's why I voted how I did. I
5 thought there were some concerns about safety, but
6 I'm not overly concerned that this would add
7 significant safety to prohibit an expanded
8 indication.

9 DR. LITMAN: Ron Litman. I voted no because
10 I wasn't convinced of the data that was presented
11 here at the FDA of both efficacy and safety. I
12 think EXPAREL's going to be an excellent local
13 anesthetic, and I would echo Dr. Terman's comments
14 before. It's just a shame that we didn't see the
15 data here today. But I think there will continue
16 to be either pre- or post-label clinical studies
17 that will be convincing, and it will, probably as
18 long as the safety data pans out, be a very widely
19 used local anesthetic someday.

20 DR. McCANN: Mary Ellen McCann. I voted no.
21 Probably the main reason is I had safety issues. I
22 actually thought that they did demonstrate some

1 efficacy, so if I didn't have the safety issues, I
2 probably would have voted yes. But I was concerned
3 about the falls, the signal of deaths, and no data
4 about rescue medications.

5 DR. GALINKIN: Jeff Galinkin. I voted no.
6 Again, I also had a concern about the efficacy and
7 some of the safety data. Further, in the future,
8 it would be nice to see some pediatric dosing
9 information as well.

10 DR. HIGGINS: Jennifer Higgins. I voted no
11 for the reasons I stated previously.

12 DR. PORTER: Laura Porter. I voted yes.

13 DR. TERMAN: Greg Terman. I voted yes with
14 the proviso that the current restriction on
15 bupivacaine within 96 hours was generalized to all
16 local anesthetics, that some preclinical lipid
17 emulsion therapy studies were done to make sure
18 there wasn't interaction between the liposomes and
19 the lipid emulsion, and finally, an active
20 comparison in the brachial plexus study to show
21 more prolonged use or benefit.

22 DR. ZACHAROFF: Hi. This is Kevin

1 Zacharoff. I voted yes, and I would echo
2 Dr. Terman's comments with respect to other
3 studies. At the end of the day, I think being that
4 this was a medication that had already been
5 approved, I think there was enough information for
6 me, from a safety and efficacy perspective, to vote
7 yes. With respect to the falls, I think a lot of
8 it has to do with what's done on an institutional
9 basis with respect to people who are at fall risk
10 and not the medication itself.

11 DR. GULUR: Dr. Gulur. I voted no for
12 reasons already stated by my colleagues and with
13 the same recommendations that my colleagues to my
14 left made even though they voted yes, that further
15 studies are required.

16 DR. McCANN: We're not going to take a break
17 now, right? We're ready to adjourn?

18 DR. HERTZ: Yes.

19 DR. McCANN: Are there any other questions
20 for the FDA or other comments for the FDA?

21 (No response.)

22 DR. HERTZ: With that, I will thank you-all

1 again. Again, we really appreciate it. We know
2 how busy you are, so thank you and safe travels
3 home.

4 **Adjournment**

5 DR. McCANN: Panel members, please take all
6 your personnel belongings with you as the room is
7 cleaned at the end of the day. All materials left
8 on the table will be disposed of. Please also drop
9 off our name badge at the registration table on the
10 way out so they may be recycled. We will now
11 adjourn this meeting. Thank you.

12 (Whereupon, at 2:56 p.m., the meeting was
13 adjourned.)

14
15
16
17
18
19
20
21
22