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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ANESTHETIC AND ANALGESIC DRUG PRODUCTS
ADVISORY COMMITTEE (AADPAC) MEETING

Thursday, January 16, 2020
8:00 a.m. to 2:46 p.m.

FDA White Oak Campus
Building 31, the Great Room
10903 New Hampshire Avenue
Silver Spring, Maryland

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4 Division of Advisory Committee and

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1 P R O C E E D I N G S

2 (8:00 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

5 DR. LITMAN: Good morning. I'm Ron Litman.
6 I'm the chair of the meeting today. I would first
7 like to remind everyone to please silence your cell
8 phones, smartphones, and any other devices if you
9 have not already done so. I would like to identify
10 the FDA press contact, Nathan Arnold.

11 Nathan, are you here? Good morning. If
12 anybody has any media inquiries or anything, please
13 ask Nathan.

14 I will now call the Joint Meeting of the
15 Anesthetic and Analgesic Drug Products Advisory
16 Committee and Drug -- nope, we're not with the Drug
17 Safety Risk Committee. That's yesterday script.
18 We'll start by going around the table and
19 introducing ourselves. We'll start with the FDA to
20 my left and go around the table. Please state your
21 name and your expertise.

22 DR. ROCA: Good morning. My name is Rigo

1 Roca. I'm acting director for the Division of
2 Anesthesiology, Addiction Medicine, and Pain
3 Medicine in the Office of Neuroscience.

4 DR. LOWY: Good morning. Naomi Lowy, acting
5 deputy director in the same division.

6 DR. PETIT-SCOTT: Good morning. Renee
7 Petit-Scott, medical officer in the same division.

8 MS. MEAKER: Kate Meaker, statistical
9 reviewer, Division of Biometrics I.

10 DR. McCANN: Hi. Mary Ellen McCann. I'm a
11 pediatric anesthesiologist at Boston Children's and
12 an associate professor of anesthesiology at Harvard
13 Medical School.

14 DR. ZACHAROFF: Good morning. My name is
15 Kevin Zacharoff. My expertise is in anesthesiology
16 and pain medicine. I am faculty, clinical
17 instructor, and course director for pain and
18 addiction at the Stony Brook School of Medicine.

19 DR. McAULIFFE: I'm Maura McAuliffe. I'm
20 professor of nursing and director of the Nurse
21 Anesthesia Program, East Carolina University.

22 DR. ZELTZER: Hi. I'm Lonnie Zeltzer,

1 distinguished professor of pediatrics,
2 anesthesiology, and psychiatry, University of
3 California Los Angeles, and director of pediatric
4 pain and palliative care program.

5 DR. GOUDRA: Hi. Good morning. I'm
6 Basavana Goudra, associate professor of
7 anesthesiology at Penn medicine, Philadelphia.

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

10 DR. LITMAN: Ron Litman. I'm an
11 anesthesiologist at the University of Pennsylvania
12 and Children's Hospital of Philadelphia and the
13 medical director of the Institute for Safe
14 Medication Practices.

15 DR. SHO BEN: Hi. I'm Abby Shoben. I'm an
16 associate professor of biostatistics at The Ohio
17 State University.

18 DR. HIGGINS: Good morning. Jennifer
19 Higgins. I'm the consumer representative to
20 AADPAC. My PhD is in gerontology and my background
21 is in clinical trials in neurology.

22 MR. O'BRIEN: Joe O'Brien, the president and

1 CEO of the National Scoliosis Foundation, and I am
2 the patient representative.

3 DR. ZAAFRAN: Sherif Zaafran,
4 anesthesiologist from Houston. I'm on the Memorial
5 Hermann Healthcare System Acute and Chronic Pain
6 Committee and vice chair of the Clinical Governance
7 Board for U.S. Anesthesia Partners.

8 DR. CULLEN: Joe Cullen, professor of
9 surgery at the University of Iowa, College of
10 Medicine.

11 DR. FALTA: Edward Falta. I'm a general
12 surgeon at West Point, New York.

13 DR. HORROW: Good morning. My name is Jay
14 Horrow. I'm an anesthesiologist. I'm the industry
15 representative to the committee. I'm a clinical
16 trial lead for cardiovascular medicines at
17 Bristol-Myers Squibb.

18 DR. LITMAN: Thanks, everybody.

19 For topics such as those being discussed at
20 today's meeting, there are often a variety of
21 opinions, some of which are quite strongly held.
22 Our goal is that today's meeting will be a fair and

1 open forum for discussion of these issues and that
2 individuals can express their views without
3 interruption. Thus, as a gentle reminder,
4 individuals will be allowed to speak into the
5 record only if recognized by the chair. We look
6 forward to a productive meeting.

7 In the spirit of the Federal Advisory
8 Committee Act and the Government in the Sunshine
9 Act, we ask that the advisory committee members
10 take care that their conversations about the topic
11 at hand take place in the open forum of the
12 meeting.

13 We are aware that members of the media are
14 anxious to speak with the FDA about these
15 proceedings, however, FDA will refrain from
16 discussing the details of this meeting with the
17 media until its conclusion. Also, the committee is
18 reminded to please refrain from discussing the
19 meeting topics during breaks or lunch.

20 Thanks. Now, I'll pass this over to Moon
21 Hee Choi, who will read the Conflict of Interest
22 Statement.

1 **Conflict of Interest Statement**

2 DR. CHOI: The Food and Drug Administration
3 is convening today's meeting of the Anesthetic and
4 Analgesic Drug Products Advisory Committee under
5 the authority of the Federal Advisory Committee Act
6 of 1972.

7 With the exception of the industry
8 representative, all members and temporary voting
9 members of the committee are special government
10 employees or regular federal employees from other
11 agencies and are subject to federal conflict of
12 interest laws and regulations.

13 The following information on the status of
14 this committee's compliance with federal ethics and
15 conflict of interest laws, covered by but not
16 limited to those found at 18 U.S.C. Section 208, is
17 being provided to participants at today's meeting
18 and to the public.

19 FDA has determined that members and
20 temporary voting members of this committee are in
21 compliance with federal ethics and conflict of
22 interest laws. Under 18 U.S.C. Section 208,

1 Congress has authorized FDA to grant waivers to
2 special government employees and regular federal
3 employees who have potential financial conflicts
4 when it is determined that the agency's need for a
5 special government employee's services outweighs
6 his or her potential financial conflict of
7 interest, or when the interest of a regular federal
8 employee is not so substantial as to be deemed
9 likely to affect the integrity of the services
10 which the government may expect from the employee.

11 Related to the discussions of today's
12 meeting, members and temporary voting members of
13 this committee have been screened for potential
14 financial conflicts of interest of their own as
15 well as those imputed to them, including those of
16 their spouses or minor children, and for purposes
17 of 18 U.S.C. Section 208, their employers.

18 These interests may include investments;
19 consulting; expert witness testimony; contracts,
20 grants, CRADAS; teaching, speaking, writing;
21 patents and royalties; and primary employment.

22 Today's agenda involves discussion of new

1 drug application, NDA, 204803, bupivacaine
2 extended-release solution for instillation,
3 submitted by DURECT Corporation, for the proposed
4 indication of postsurgical analgesia.

5 The committee will discuss whether the
6 applicant adequately demonstrated the safety and
7 efficacy of bupivacaine extended-release solution
8 for postsurgical analgesia and the appropriateness
9 of the proposed patient populations. The committee
10 will also be asked to discuss the approvability of
11 this product.

12 This is a particular matters meeting during
13 which specific matters related to DURECT's NDA will
14 be discussed. Based on the agenda for today's
15 meeting and all financial interests reported by the
16 committee members and temporary voting members, no
17 conflict of interest waivers have been issued in
18 connection with this meeting.

19 To ensure transparency, we encourage all
20 standing committee members and temporary voting
21 members to disclose any public statements that they
22 have made concerning the product at issue.

1 With respect to FDA's invited industry
2 representative, we would like to disclose that
3 Dr. Jay Horrow is participating in this meeting as
4 a nonvoting industry representative, acting on
5 behalf of regulated industry. Dr. Horrow's role at
6 this meeting is to represent industry in general
7 and not any particular company. Dr. Horrow is
8 employed by Bristol-Myers Squibb.

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

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

20 DR. LITMAN: Thanks, Moon.

21 We will now proceed with the FDA's
22 introductory remarks from Dr. Rigoberto Roca.

1 **FDA Introductory Remarks - Rigoberto Roca**

2 DR. ROCA: Good morning. Mr. Chairman,
3 members of the committee, and invited guests,
4 welcome. My name is Rigo Roca. I'm acting
5 director of the Division of Anesthesiology,
6 Addiction Medicine, and Pain Medicine. Today we
7 will be discussing the product Posimir, which, as
8 noted in the background package, is bupivacaine
9 formulation in a special sucrose polymer. The
10 indication has been read by Dr. Choi, and what I
11 would like to do is just briefly go over some other
12 things that I would like the committee to focus on.

13 Just briefly, with respect to the agenda,
14 after the presentation by the company and the
15 break, there will be an FDA presentation, and the
16 FDA presentation will consist of two people.

17 Dr. Petit-Scott will be speaking to the
18 current postsurgical analgesic treatment options
19 and summary of the clinical development program.
20 She will be followed by Ms. Meaker, who is our
21 statistical reviewer on the application, who will
22 discuss the statistical review of the efficacy

1 data. Then Dr. Petit-Scott will come back and
2 speak to the clinical implication of efficacy data,
3 as well as an assessment of safety data from
4 studies in support of the NDA.

5 As was noted in the briefing package, this
6 particular drug development program has had a long
7 history with the IND actually being submitted back
8 in 2002. Over the course of the years, we've had
9 several interactions with the company, and the
10 regulatory history has included submission of an
11 NDA; a complete response after that submission; a
12 request by the company to have a dispute
13 resolution; and then, subsequently, a resubmission
14 with data from a new study intended to address the
15 issues identified in the complete response, as well
16 as items identified in the dispute resolution
17 letter from the office.

18 As you can imagine, in a drug development
19 program that has spanned almost 17 years, there
20 have been several clinical trials, and there is a
21 need and a desire to organize the data into
22 different forms. You can make lots of reasonable

1 schemes of how that should be arranged. There
2 could be phase studies, phase 2, phase 3. They
3 could be arranged with respect to the procedures,
4 the surgical anatomical site, the intent of the
5 study, the purpose, primary, supportive, et cetera,
6 and exploratory.

7 I think it's important to do that in order
8 to assimilate all the information that you're going
9 to be looking at. However, terms are sometimes
10 helpful, but they can also sometimes confuse the
11 issue. For example, the term "pivotal," should a
12 pivotal study be one that has demonstrated efficacy
13 and safety for Posimir or should a pivotal study
14 actually be a study that was designed to assess
15 efficacy and safety regardless of what the results
16 were?

17 One of the things I think will be important
18 as you look at the information, the background and
19 the presentations today, is to, yes, of course be
20 cognizant of the different identifications and the
21 different trials. But in reality, as to whether
22 the information from the trials and whether the

1 trials were adequately designed to generate data
2 that you can then utilize to assess the efficacy
3 and safety of the program, I think that that will
4 be probably as important, if not more, as to what
5 it is called.

6 So to that end, let's turn to the first
7 discussion point. As is often the case with items
8 brought to this committee, the question may seem
9 relatively simple and straightforward; the answer
10 perhaps not, and that is whether there's sufficient
11 information in the application to support the
12 proposed indication that, as mentioned before,
13 Dr. Choi read.

14 Second, as you listen to the information,
15 the second point of discussion would be whether
16 there are any issues with this resubmission and
17 with respect to the complete response that would
18 require additional information and additional
19 studies, and whether these studies should be
20 conducted before or after approval.

21 As has been done by the committee before,
22 when you take all of the information presented, we

1 go to the third discussion point, which is whether
2 the efficacy, and safety, and overall risk-benefit
3 profile of the product, Posimir, support the
4 approval of this application, taking into account
5 everything that you've heard today.

6 Then lastly, we will have a voting question.
7 This voting question, as we've done before, is
8 whether you recommend approval of Posimir for the
9 indication as noted. If you do vote yes, discuss
10 your rationale and specify whether you feel that
11 there are any post-approval studies that should be
12 required. Similarly, if you vote no, please
13 discuss the rationale and any additional data you
14 feel are needed to permit approval.

15 I thank you, and I'm looking forward to an
16 informative meeting. Thanks.

17 DR. LITMAN: Thanks, Rigo.

18 Both the Food and Drug Administration and
19 the public believe in a transparent process for
20 information gathering and decision making. To
21 ensure such transparency at the advisory committee
22 meeting, FDA believes that it is important to

1 understand the context of an individual's
2 presentation.

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

11 Likewise, FDA encourages you at the
12 beginning of your presentation to advise the
13 committee if you do not have any such financial
14 relationships. If you choose not to address this
15 issue of financial relationships at the beginning
16 of your presentation, it will not preclude you from
17 speaking.

18 We will now proceed with DURECT
19 Corporation's presentation.

20 **Applicant Presentation - Neil Verity**

21 DR. VERITY: Good morning. My name is
22 Dr. Neil Verity, and I am the executive director of

1 pharmacology as well as the SABER bupivacaine
2 project team leader at DURECT Corporation. As
3 such, my first duty today is to thank the
4 Anesthetic and Analgesic Drug Products Advisory
5 Committee and the FDA for the opportunity to speak
6 to you today regarding our investigational new drug
7 product, SABER-bupivacaine, referred to as Posimir
8 in the opening remarks by the FDA.

9 A quick agenda, in the next 90 minutes, a
10 number of speakers, including myself, will present
11 various aspects of the SABER-bupivacaine
12 development program, a product designed to treat
13 acute postoperative incisional pain by providing
14 continuous release of bupivacaine at the surgical
15 site for 72 hours.

16 As shown on the slide, we will start with
17 Dr. Gan, who will put the value, benefit, and need
18 for SABER bupivacaine into clinical context. I
19 will then as an introduction give a brief overview
20 of the SABER-bupivacaine program. Dr. Jon Meisner
21 of DURECT will then present the totality of our
22 efficacy and safety data.

1 We will then close with testimony from two
2 physicians who have firsthand clinical trial
3 experience with SABER-bupivacaine, Dr. Asok
4 Doraiswamy, a surgeon, and Dr. Harold Minkowitz, an
5 anesthesiologist, both of whom will give personal
6 perspectives on their experience with the use of
7 SABER bupivacaine. Finally, this next slide lists
8 the experts we have with us to answer specific
9 questions from the committee.

10 With that said, I'd now like to turn the
11 podium over to Dr. Gan.

12 **Applicant Presentation - Tong Gan**

13 DR. GAN: Good morning. I'm TJ Gan,
14 professor and chairman of the Department of
15 Anesthesiology at Stony Brook School of Medicine,
16 and also a practicing anesthesiologist. I would
17 like to disclose that I serve as a consultant to
18 DURECT and have received honoraria and
19 reimbursement of travel expenses.

20 I have spent most of my career in clinical
21 research and have served as a principal
22 investigator in more than a hundred clinical

1 trials. I'm here today to discuss what I believe
2 is one of the most significant needs in the
3 analgesic space, the need for non-opioid options
4 that provide durable pain control and lessen or
5 avoid the need for opioids.

6 More than 50 million surgical procedures are
7 performed each year in the United States with up to
8 70 percent of patients experiencing moderate to
9 severe pain following surgery. Effectively
10 treating post-op pain is essential, as we know that
11 poorly controlled pain following surgery can result
12 in multiple negative outcomes and delayed
13 discharge.

14 A multimodal analgesic regimen relies on a
15 combination of pharmacological and
16 nonpharmacological modalities, enhanced recovery
17 after surgery, or ERAS, E-R-A-S, protocols, and
18 embracing multimodal analgesic regimens have shown
19 to help reduce opioid use while improving outcomes
20 and enhancing patient experience.

21 Up to 78 percent of patients are
22 administered a local anesthetic during surgery for

1 pain control, and as part of a multimodal regimen,
2 it is a relatively simple and safe means of
3 providing postoperative pain relief. However,
4 there are a few challenges with currently available
5 local anesthetics.

6 Although we have many local anesthetics,
7 they are insufficient to provide prolonged
8 analgesia. As opposed to lidocaine, longer-acting,
9 immediate-release local anesthetics like
10 bupivacaine and ropivacaine last about 8 hours, and
11 the extended-release local anesthetic liposomal
12 bupivacaine extends the duration of pain relief for
13 up to 24 hours. That means that patients are often
14 left with uncontrolled pain on days 2 and 3
15 following their surgery, and physicians and
16 patients often turn to opioids as rescue medication
17 to provide pain relief.

18 It is estimated that up to 90 percent of
19 patients who undergo surgery are given opioids for
20 treatment of moderate to severe pain in the
21 immediate postoperative period as well as critical
22 care settings, although effective opioids can be

1 associated with adverse events, including
2 postoperative nausea and vomiting, constipation,
3 sedation, and respiratory depression, which can
4 prolong a patient's hospital stay.

5 Now, as you are aware, we are facing an
6 opioid crisis in this country. One review showed
7 that patients who receive an opioid prescription
8 within 7 days of a short-stay surgery were
9 44 percent more likely to become long-term opioid
10 users. Another study showed that 6 percent of
11 patients who were prescribed opioids
12 perioperatively continued to use them at 90 to 180
13 days compared with 0.4 percent of controls.

14 Now, this equates to more than 2 million
15 persistent postoperative opioid users each year.
16 Hence, the development of a long-acting, non-opioid
17 analgesic is both a clinical goal and a public
18 health goal.

19 Specifically, we need a local anesthetic
20 that can be used broadly across surgical procedures
21 with effective sustained pain relief for a longer
22 period following surgery. If available, such an

1 agent would be the foundation of a multimodal
2 regimen to promote opioid-free analgesia, reducing
3 opiate-related adverse effects to the patients,
4 consistent with the ERAS principles and potentially
5 reducing risks to society of overprescription and
6 abuse of opioids and misuse.

7 Thank you for your attention. I will now
8 turn the lectern over to Dr. Verity.

9 **Applicant Presentation - Neil Verity**

10 DR. VERITY: Thank you, Dr. Gan.

11 Once again, my name is Dr. Neil Verity, and
12 I am the executive director of pharmacology at
13 DURECT Corporation. As mentioned by Dr. Gan, even
14 to this day, acute postoperative pain remains a
15 significant challenge for patients, hospital staff,
16 care providers, and immediate family members. To
17 this end, SABER-bupivacaine has been designed to
18 treat acute postoperative pain by providing
19 continuous release of bupivacaine, a well-known
20 local anesthetic, at the surgical site for 72
21 hours.

22 To set the stage, I'd like to go over a few

1 key SABER-bupivacaine development goals. First is
2 the indication, so let me take a moment to be clear
3 since there is some discussion about this in the
4 FDA briefing book.

5 We, DURECT Corporation, the sponsor, are
6 seeking an indication that reads, "For single-dose
7 instillation into the surgical site to produce
8 postsurgical analgesia with the intention that
9 SABER-bupivacaine will be used in a variety of
10 surgical procedures." As mentioned a few times,
11 SABER-bupivacaine's mode of action is that of an
12 extended-release bupivacaine formulation.

13 In terms of administration,
14 SABER-bupivacaine also has a unique mode of
15 administration in that it is typically administered
16 at the end of surgery as a single 5 mL dose via a
17 needle-free technique directly instilling
18 SABER-bupivacaine into the surgical incision.

19 I'll have a little more data on this in a
20 few slides. However, having just said that, due to
21 its solution nature, SABER-bupivacaine can be
22 injected through a large bore needle into unique,

1 anatomic spaces under visual guidance if desired.

2 The efficacy goal of the SABER-bupivacaine
3 program is to provide continuous 72-hour pain
4 reduction, covering the peak period of postsurgical
5 pain. Again, to be clear, our clinical development
6 program was designed to show efficacy over placebo
7 as per regulatory requirements, but as you'll see
8 later, in some cases we have also enlisted
9 bupivacaine hydrochloride as an active comparator.

10 In terms of safety goals, SABER-bupivacaine
11 was engineered to assure a stable release of
12 bupivacaine over 3 days while ensuring no dose
13 dumping, thereby assuring safe systemic levels.
14 Finally, administration of SABER-bupivacaine should
15 not impact normal incision wound healing. In
16 summary, taken together, the goal of the
17 SABER-bupivacaine program is to add a long-lasting,
18 non-opioid analgesic to the multimodal analgesic
19 toolbox.

20 Now, let's spend a moment on the formulation
21 itself. SABER-bupivacaine is a clear, light amber
22 in color, room temperature, stable solution

1 composed of three components. The first component
2 is the active pharmaceutical ingredient, or API,
3 bupivacaine base, an amide-type local anesthetic
4 first approved as a hydrochloride salt in the early
5 '70s.

6 A single 5 mL dose of SABER-bupivacaine
7 contains bupivacaine base at a concentration of
8 13.2 percent or 132 mgs per mL for a total dose of
9 660 milligrams. The relatively high-drug load
10 ensures sufficient amounts of bupivacaine for
11 sustained release over 72 hours, equivalent to 743
12 milligrams of bupivacaine hydrochloride.

13 The second component is the novel excipient
14 SAIB, or sucrose acetate isobutyrate. SAIB is a
15 high viscosity, hydrophobic, non-polymeric,
16 biocompatible and biodegradable, fully esterified
17 sucrose moiety. Once administered, SAIB is
18 responsible for the retention and release of
19 bupivacaine.

20 Note that as a food additive, for instance
21 as a densifying agent in citrus-flavored beverages,
22 SAIB enjoys GRAS, or generally regarded as safe,

1 status with an ADI, allowable daily intake, of 20
2 mgs per kg established by the World Health
3 Organization.

4 The third and final component is benzyl
5 alcohol at 22 percent, equivalent to 1.2 mL per
6 dose of SABER-bupivacaine. Benzyl alcohol when
7 mixed with SAIB causes the viscosity of SAIB to
8 drop tremendously while maintaining bupivacaine
9 base in solution. This drop in viscosity allows
10 for controlled instillation directly into the
11 surgical site.

12 Once SABER-bupivacaine is instilled within
13 the surgical site, the benzyl alcohol rapidly
14 diffuses away, increasing the viscosity of the
15 remaining SABER-bupivacaine mixture, allowing it to
16 set up as an in situ forming depot, controlling the
17 release of bupivacaine.

18 As mentioned and shown here in yellow on the
19 left, SABER-bupivacaine is administered by the
20 surgeon as a single 5 mL dose at the end of
21 surgery, typically just prior to skin closure.
22 Unlike bupivacaine hydrochloride, shown on the

1 right, it is not infiltrated into tissue
2 surrounding an incision, but rather instilled
3 directly into the surgical incision with a
4 needle-free syringe or other blunt-tipped
5 applicator.

6 This instillation directly into the wound
7 assures bupivacaine is placed where it is most
8 effective while also avoiding possible inadvertent
9 intravascular injection due to blind tissue
10 infiltration, as can occur with current
11 short-acting aqueous local anesthetics.

12 In cases where the surgical site may not be
13 directly accessible, for example the subacromial
14 space in our shoulder arthroscopic trial which
15 you'll hear about shortly, the drug may also be
16 injected into the targeted anatomic space under
17 direct visual guidance, for instance using an
18 arthroscope.

19 This next slide shows the bupivacaine
20 release rate from SABER-bupivacaine 5 mL injected
21 into healthy volunteers. SABER-bupivacaine has
22 been formulated to deliver bupivacaine at a rate of

1 10 to 20 milligrams per hour, consistent with
2 published local anesthetic delivery rates known to
3 be efficacious across a variety of surgical
4 procedures using wound catheters and external
5 pumps; and this is represented by the gray shaded
6 area on the slide.

7 As can be seen, the release rate of
8 SABER-bupivacaine, the solid line, is 1) continuous
9 over 72 hours; 2) within the target range of 10 to
10 20 mgs per hour, and 3) displays no evidence of
11 dose dumping upon administration.

12 The pharmacokinetics of SABER-bupivacaine
13 has been studied across multiple surgical
14 procedures, utilizing a wide range of incision
15 lengths and anatomic locations. As shown here,
16 looking at plasma bupivacaine levels, a consistent
17 pattern is observed over 3 days with slight
18 differences in plasma profiles between different
19 surgical procedures, presumably due to
20 differences in local tissue vascularity as well as
21 fat content.

22 While the Tmax varies along a continuum from

1 about 4 hours in shoulder surgery to 48 hours in
2 major abdominal surgery, the peak plasma
3 concentrations all fall within a relatively narrow
4 band that tops out at less than 900 nanograms per
5 mL.

6 Now, if we compress the presented plasma
7 curves and highlight the generally agreed upon
8 published systemic toxicity range, shown here in
9 gray on the slide, we see that all the mean
10 SABER-bupivacaine plasma of curves are well below
11 the systemic toxic range. Furthermore, if we plot
12 the individual patients with Cmaxes greater than
13 1000 nanograms per mL, we see that they are all
14 still below the toxicity range.

15 The SABER-bupivacaine clinical program was
16 extensive, with a total of 14 studies with 876
17 subjects exposed to SABER-bupivacaine across
18 numerous surgical procedures with over 1400
19 subjects in total. As we'll discuss in a moment,
20 not all of these studies produced valid efficacy
21 data, however, as a whole, they did provide
22 valuable learnings and inform our understanding of

1 the SABER-bupivacaine safety profile.

2 To expand on the previous slide,
3 SABER-bupivacaine has been studied in a wide range
4 of surgical procedures with the goal of
5 demonstrating suitability for general use. There
6 were 6 soft tissue surgical models and 1 orthopedic
7 surgical model. Four of these surgeries were
8 performed with open incisions, two utilizing
9 endoscopic ports, and one combined procedure using
10 both an incision and a laparoscopic port.

11 Of these surgeries, 4 were more invasive
12 inpatient procedures and 3 were less invasive
13 outpatient procedures. Overall, the cumulative
14 incision lengths ranged from a low of 2 centimeters
15 to a high of 40 centimeters.

16 At this point, I'd like to preview the
17 important points we will communicate to you in the
18 remainder of this presentation. The efficacy of
19 SABER-bupivacaine has been demonstrated in two
20 pivotal trials and further supported by additional
21 adequate and well-controlled trials.

22 Reduced opioid use and delayed time to first

1 opioid use support the clinical relevance of the
2 observed analgesic effects of SABER-bupivacaine.
3 Meta-analysis suggests SABER-bupivacaine as being
4 more effective than immediate-release bupivacaine
5 hydrochloride. SABER-bupivacaine has been shown to
6 be safe and effective across numerous surgical
7 procedures.

8 In terms of safety, a new study, PERSIST,
9 and a new compilation of the integrated summary of
10 safety, or ISS, demonstrate, with the exception of
11 bruise-like discoloration, that there is no
12 appreciable increased risk of adverse events, local
13 anesthetic, systemic toxicity, or last, wound
14 healing complications or chondrolysis, and no
15 benzyl alcohol toxicity. As such, we now believe
16 an appropriate risk-benefit assessment can be
17 performed supporting the approval of
18 SABER-bupivacaine.

19 I'll now like to turn the podium over to
20 Dr. Jon Meisner, executive director of clinical
21 development at DURECT, who will present the bulk of
22 this presentation as he describes the results from

1 our clinical trials, demonstrating the safety and
2 efficacy of SABER-bupivacaine. Dr. Meisner?

3 **Applicant Presentation - Jon Meisner**

4 DR. MEISNER: Good morning. I'm Dr. Jon
5 Meisner. I'm the executive director of clinical
6 development at DURECT, and my clinical background
7 is anesthesiology. I'm going to review the data
8 supporting the efficacy and safety of
9 SABER-bupivacaine, and to begin I'd like to briefly
10 review some relevant regulatory history and also
11 make clear the important differences between the
12 FDA's briefing book and our briefing book.

13 The objective of this clinical program was
14 to establish the efficacy of SABER-bupivacaine
15 relative to placebo control, not relative to
16 bupivacaine, which is the reference drug. Although
17 there were some trials that had bupivacaine HCl
18 control arms, none of our studies were designed for
19 a primary comparison with active control.

20 Per agency guidance, we sought to establish
21 efficacy in at least one soft tissue surgical model
22 and one orthopedic, or bony, model to demonstrate

1 the suitability of our product for general surgical
2 use as a local analgesic to treat incisional pain.

3 The efficacy results of our two pivotal
4 trials were submitted with our original NDA in
5 2013, and the complete response letter we received
6 in 2014 did not question these two trials'
7 demonstration of efficacy. The division, however,
8 did raise concerns about the consistency and degree
9 of efficacy and about three specific safety issues,
10 which I will discuss in detail during the course of
11 this presentation.

12 The data I will present on the safety and
13 efficacy of SABER-bupivacaine is the most up to
14 date, reliable, and relevant data, bearing on the
15 questions the division has asked you to consider
16 during this meeting. Our 2019 complete response to
17 the complete response letter issued in 2014
18 included a thorough reanalysis of all our efficacy
19 and safety data, along with incorporation of the
20 results of an entirely new laparoscopic
21 cholecystectomy study into the data set.

22 We developed this response to deal with the

1 areas of our original submission that the agency
2 informed us were unclear, confusing, or
3 insufficient. Our updated 2019 submission,
4 reflected in the briefing document we prepared for
5 you but much less so in the FDA's briefing
6 document, included an entirely new integrated
7 summary of efficacy and the integrated summary of
8 safety, both of which are critical in evaluating
9 the totality of evidence demonstrating the efficacy
10 and safety of our product. So should you have any
11 questions regarding the approach we took, we'll be
12 happy to address them during the Q&A session.

13 Now, let's examine the data supporting the
14 efficacy of SABER-bupivacaine. As part of our work
15 to address the FDA's complete response letter, we
16 systematically reviewed the efficacy trials we had
17 conducted to determine which were adequate and well
18 controlled and which were not.

19 To perform this review, we used the criteria
20 from the U.S. Code of Federal Regulations,
21 paraphrased here, that the agency itself applies to
22 determine the suitability of clinical trials to

1 support product efficacy. Using a standardized
2 checklist, we evaluated each of the efficacy trials
3 in our clinical program for compliance with these
4 standards.

5 You may wonder why we undertook this
6 exercise. As you know, adequate and
7 well-controlled studies can be used to establish
8 the efficacy of an investigational product, whereas
9 studies that did not rise to that level of rigor
10 cannot provide data either to support or to refute
11 the product's efficacy.

12 By failing to undertake such a systematic
13 review in advance of our previous 2013 submission,
14 we inappropriately allowed some data from
15 poor-quality trials to mix into the overall
16 efficacy assessment, which contributed to the
17 division's inability to formulate a benefit-to-harm
18 assessment.

19 You may also ask why all the studies in our
20 clinical program were not adequate and well
21 controlled, and here's the answer. During the
22 course of clinical research, particularly early on,

1 studies may be conducted to explore the dose, mode
2 of administration, disease models, study designs,
3 endpoints, et cetera, that will best elucidate the
4 properties of the investigational product, and
5 these learning experiences may not be adequate and
6 well controlled.

7 Nonetheless, they contribute valuable
8 hypothesis-forming information and important safety
9 results to the development plan. However, the
10 results should not be regarded in the same light as
11 those derived from adequate and well-controlled
12 confirmatory studies performed later in the
13 development program.

14 Our evaluation of the 11 efficacy trials in
15 the SABER-bupivacaine clinical program established
16 that six were adequate and well controlled and five
17 were not. Two of the adequate and well-controlled
18 trials are designated as pivotal and four as
19 supportive.

20 In the next few slides, I'd like to explain
21 in detail why these two studies in inguinal hernia
22 repair and laparoscopic cholecystectomy cannot be

1 considered adequate and well controlled. I'm
2 selecting these two studies because the FDA
3 presents their efficacy results in such a way as to
4 suggest they are of similar quality, as the six
5 adequate and well-controlled studies on the left,
6 and therefore can be used to undermine conclusions
7 of efficacy generated by our two positive trials.

8 First, the 005-0010 trial, there were a
9 total of 5 trials that we performed an inguinal
10 hernia repair, and the first 4, including this one,
11 were early learning experiences that helped us
12 develop a better understanding of the safest and
13 most effective way to use our novel product in this
14 surgical model. These experiences were followed by
15 a fifth inguinal hernia repair trial that was
16 intended to confirm what had been learned, and this
17 trial was in fact our pivotal soft tissue trial.

18 During this early learning experience,
19 2 doses and 3 modes of administration of
20 SABER-bupivacaine were explored. While this trial
21 generated valuable insights, there were numerous
22 inadequacies in design, conduct, and analysis,

1 listed on the table on this slide, that make it
2 impossible to judge it as an adequate and
3 well-controlled trial for purposes of confirming or
4 rejecting efficacy; and I do invite you during the
5 Q&A session to explore our contention that this was
6 not an adequate and well-controlled trial further.

7 Any efficacy results derived from this
8 trial, especially those figuring into the FDA's
9 2013 overall efficacy conclusions, cannot be
10 compared on an equal footing with results derived
11 from our successful pivotal hernia repair trial,
12 which I'll describe momentarily.

13 The laparoscopic cholecystectomy trial,
14 803-028, also known as PERSIST, was conducted after
15 receipt of the 2014 complete response letter and
16 formal dispute resolution, and was intended to add
17 comparative safety data versus a non-SABER
18 containing control, saline placebo, as the agency
19 had requested.

20 The problem with this study arises with the
21 agency's subsequent request to compare
22 SABER-bupivacaine with bupivacaine HCl, which was

1 communicated to us well after the trial had begun
2 enrolling patients. In response, we switched the
3 control comparator from saline to bupivacaine HCl,
4 renamed the terminated saline-controlled portion of
5 the trial Part 1, and called the bupivacaine HCl
6 controlled portion of the trial Part 2.

7 The trial was not stopped and restarted;
8 rather, a protocol amendment was transmitted to
9 each of the investigative sites, announcing a
10 switch in control of comparator and implementation
11 of a new randomization scheme. To compensate for
12 reduced study power in comparing SABER-bupivacaine
13 with an active control, we changed the primary
14 evaluation period from 72 hours to 48 hours, a
15 departure from our previous adequate and
16 well-controlled studies.

17 During the course of Part 2, we continued to
18 receive periodic requests from the agency for
19 substantive changes to the protocol, most of which
20 required IRB approval, retraining of the
21 investigators, and new informed consent language.
22 In my opinion, when you have multiple

1 non-prospectively planned substantive midstream
2 changes to a protocol, you cannot rely upon that
3 study to accurately measure the efficacy of an
4 analgesic product. Since Part 2 was an amended
5 continuation of Part 2, it cannot be considered a
6 stand-alone trial.

7 Now, that I've covered these important
8 contextual points, let's start with an overview of
9 the six adequate and well-controlled efficacy
10 studies in our data set; first, some common design
11 elements.

12 All were randomized-controlled trials.
13 Subjects recorded pain on movement in electronic
14 diaries at prespecified intervals. Unlike in
15 chronic pain trials, no baseline postsurgical
16 scores were recorded in any of our studies because
17 the drug as intended was administered under
18 anesthesia in the operating room. All subjects
19 were provided with systemic opioids upon request
20 for breakthrough pain, and the times and doses were
21 recorded.

22 The primary evaluation period for

1 postoperative pain was 72 hours, which was the
2 expected duration of action of the investigational
3 agent. Mean pain on movement over 72 hours was the
4 primary efficacy endpoint for all trials. Several
5 different measures of opioid use were included as
6 co-primary or secondary endpoints. These included
7 the percentage of subjects in each treatment group
8 that used opioids during the designated evaluation
9 period, the cumulative dose of opioid rescue
10 medication consumed over the same period, and the
11 time to first use of opioid rescue medication.

12 For the two adequate and well-controlled
13 studies with bupivacaine HCl active control arms,
14 all comparisons with bupivacaine HCl were
15 prespecified as exploratory. The efficacy
16 population of the six adequate and well-controlled
17 studies included a total of 699 subjects across
18 multiple surgical models of which 373 were
19 administered SABER-bupivacaine 5 mL.

20 Now, let's examine the two pivotal studies.
21 The first pivotal trial was a soft tissue model,
22 open mesh, inguinal hernia repair. There were

1 2 dose cohorts in this trial, a 5 mL cohort, which
2 is the dose recommended for clinical use, and a
3 2-and-a-half mL cohort that was intended to better
4 characterize the dose-response relationship.
5 Tramadol or acetaminophen, depending on pain
6 severity, were the rescue analgesics available for
7 breakthrough pain.

8 There were 122 subjects in the efficacy
9 population with the final 3 to 2 randomization
10 between SABER-bupivacaine and placebo. The mean
11 age was close to 50 years and nearly all subjects
12 were male, consistent with the approximately
13 90 percent male prevalence of inguinal hernia.

14 The primary endpoint results are presented
15 here. The blue curve depicts the mean pain scores
16 recorded for the SABER-bupivacaine group over
17 72 hours, and the red curve, the pain score is
18 recorded for the placebo group. Visual separation
19 between the two curves over the entire 72-hour
20 period suggests a longitudinal treatment effect
21 with a notably strong benefit during the first 24
22 hours. The mean 72-hour pain reduction with

1 SABER-bupivacaine treatment was 1.14 on the 0 to 10
2 scale, with a significant p-value of 0.003.

3 Here I've added the pain curve for the 2 and
4 a half mL dose of SABER-bupivacaine, the dotted
5 blue line. It is apparent that this dose contained
6 insufficient bupivacaine to provide analgesia for
7 more than a 12- to 24-hour period compared with
8 placebo. Averaged over 72 hours, the point
9 estimate for pain reduction for the 2 and a half mL
10 SABER-bupivacaine was about half that of the 5 mL
11 dose, suggesting an approximately linear dose
12 response in this dose range and supporting 5 mL as
13 the recommended dose.

14 Here's a Kaplan-Meier plot of the time to
15 first use of opioid rescue. This graph indicates
16 that at 15 days post-surgery, nearly half of
17 SABER-bupivacaine treated subjects had not required
18 any opioids at all compared with 28 percent of the
19 placebo group. Further, it illustrates that the
20 median first request for opioids came at nearly 60
21 hours for subjects treated with SABER-bupivacaine
22 5 mL, whereas opioids were requested by those in

1 the placebo group at only 2.7 hours.

2 This result is important, first, because the
3 time to first use of rescue medication is
4 considered a strong indicator of the duration of
5 analgesia, and second, because it lends credibility
6 to the notion that the postsurgical use of opioids
7 can indeed be delayed, and even prevented, with
8 effective analgesic therapy.

9 When we add up all the opioid use over 15
10 days, which was the prespecified evaluation
11 interval for the opioid use endpoints in this
12 trial, the data show a reduction in opioid use for
13 the SABER-bupivacaine group compared with the
14 placebo group that was consistent with the time to
15 first use analysis. We interpret these reductions
16 in postsurgical opioid use as demonstrating the
17 clinical relevance of the reduction in pain shown
18 by the primary endpoint.

19 The second pivotal trial was an orthopedic,
20 or bony model, arthroscopic subacromial
21 decompression, a common outpatient shoulder
22 surgery. This trial had three arms,

1 SABER-bupivacaine, placebo, and conventional
2 bupivacaine HCl, each of which was instilled into
3 the subacromial space at the end of surgery under
4 direct arthroscopic visualization to ensure correct
5 placement next to the resected bone and not
6 anywhere near the joint capsule.

7 The primary comparison was between
8 SABER-bupivacaine and placebo. The comparison
9 between SABER-bupivacaine and bupivacaine HCl was
10 not powered for efficacy and was prespecified as
11 exploratory. IV or oral morphine was given upon
12 request for breakthrough pain and acetaminophen was
13 given to all subjects at 6-hour intervals around
14 the clock, as you might expect to see in a clinical
15 practice setting.

16 MRIs and examinations of shoulder function
17 were obtained at baseline and 6 months as part of
18 the safety assessment, which I'll discuss later in
19 this presentation. There were 107 subjects in the
20 efficacy population with a 2 to 1 randomization
21 between SABER-bupivacaine and placebo. The mean
22 age was 50 years, and 60 percent of the subjects

1 were women.

2 The primary endpoint results are presented
3 here. As with the hernia trial, there was visual
4 separation between the blue SABER-bupivacaine pain
5 curve and the red placebo curve over the entire
6 72 hours, again, suggesting a longitudinal
7 treatment effect. Treatment with SABER-bupivacaine
8 compared with placebo control in this higher
9 severity pain model resulted in a mean reduction in
10 pain of 1.27 over 72 hours on the 0 to 10 scale
11 with a significant p-value of 0.012.

12 For completeness, here is the pain curve for
13 the bupivacaine HCl arm. Although the comparison
14 was exploratory, it appears that SABER-bupivacaine
15 may have improved pain control compared with
16 bupivacaine HCl over the initial 12 to 24 hours
17 after surgery, as shown by the corresponding deeper
18 dip in the pain curve.

19 The median 72-hour cumulative consumption of
20 opioids was 3 times lower in the SABER-bupivacaine
21 group than the placebo group, which again supports
22 the interpretation that the pain reduction seen

1 with SABER-bupivacaine treatment in this trial was
2 clinically meaningful.

3 Following this shoulder procedure, the
4 median first request for rescue opioids came at a
5 little over 12 hours for subjects treated with
6 SABER-bupivacaine compared with a little over
7 1 hour for subjects in the placebo group, and at 72
8 hours, this delay in starting opioids translated
9 into 40 percent of SABER-bupivacaine treated
10 subjects not having required any opioids compared
11 with 16 percent of those in the placebo arm.

12 Now that we've examined the two pivotal
13 trials, let's take a look at the collective
14 evidence of efficacy. As previously noted, there
15 were an additional four efficacy trials in a
16 variety of surgical models that were adequate and
17 well controlled. These are supportive in that they
18 provided valuable additional information and added
19 to the weight of evidence favoring
20 SABER-bupivacaine efficacy.

21 Here's a forest plot showing the point
22 estimates and 95 percent confidence intervals of

1 the primary pain endpoints for each of the adequate
2 and well-controlled trials. Using that analysis,
3 we calculated an estimate of the overall analgesic
4 effect, shown in blue at the bottom, for the six
5 trials combined. The improvement in pain was
6 clearly positive in favor of SABER-bupivacaine over
7 placebo control with no crossing of the unity line.

8 Here's a forest plot showing the 72-hour
9 opioid use endpoints and 95 percent confidence
10 intervals from each of the adequate and
11 well-controlled trials. The overall reduction in
12 opioid use, in blue at the bottom, supports our
13 view that the analgesic effect seen in the previous
14 plot was clinically meaningful.

15 To round out the picture, here are several
16 additional measures of efficacy. This slide shows
17 the distribution of pain scores collected over 72
18 hours from the combined efficacy population of the
19 two pivotal trials. All pain scores, nearly 2500,
20 were sorted according to pain intensity and
21 treatment group, and the percentage of pain scores
22 at each intensity level are shown in red on the

1 left for placebo-treated subjects and in the blue
2 on the right for SABER-bupivacaine treated
3 subjects.

4 If you look at the top row, 8 and a half
5 percent of all pain scores reported by subjects in
6 the placebo group are 10's compared with 2.2
7 percent of all pain scores reported by subjects in
8 the SABER-bupivacaine group. One can see that the
9 overall effect of SABER-bupivacaine treatment was
10 to shift pain intensity downward from higher levels
11 to lower levels.

12 In fact, if you sum up the percentages in
13 each of the three pain categories -- shown on the
14 right, severe, moderate, and mild -- you find that
15 the percentage of mild pain reports was larger in
16 the SABER-bupivacaine arm than in the placebo arm,
17 and conversely, the percentage of severe pain
18 reports was smaller. Thus, there appears to be a
19 positive analgesic effect across the entire
20 spectrum of postsurgical pain during the initial 72
21 hours after treatment.

22 Now, the next question is how do we know the

1 effect lasts for a full 72 hours? We can start by
2 reviewing the pain over time graphs from the two
3 pivotal trials. As you recall, there was visual
4 separation between the SABER-bupivacaine and
5 placebo curves throughout the 72-hour period with
6 an even more pronounced difference during the
7 initial 24 hours. However, neither of these
8 studies was powered to do a point-by-point
9 statistical comparison.

10 To increase statistical power, we pooled
11 data from all six of the adequate and
12 well-controlled efficacy trials in this post hoc
13 analysis. This graph shows that the resulting
14 separation in mean pain scores extended through
15 72 hours, suggesting that SABER-bupivacaine reduced
16 pain over this entire critical period.

17 Now, as I mentioned up front, there were no
18 adequate and well-controlled comparisons in our
19 data set between SABER-bupivacaine and
20 immediate-release bupivacaine. I would, however,
21 like to present some exploratory analyses with the
22 appropriate caveats and precautions regarding the

1 conclusions that can be drawn from these data.

2 There were five trials in a variety of
3 surgical models that had bupivacaine HCl arms.
4 Here's a forest plot showing point estimates and 95
5 percent confidence intervals for the five
6 bupivacaine HCl comparisons in our clinical data
7 set. The point estimates favor SABER-bupivacaine
8 over bupivacaine HCl, and the upper bound of the 95
9 percent confidence interval for the overall
10 treatment effect, in blue at the bottom, lies at
11 0.01. This exploratory meta-analysis raises the
12 possibility that SABER-bupivacaine may provide
13 improvement over bupivacaine HCl when averaged over
14 the 72-hour measurement interval.

15 Now, here's a comparative look at pain over
16 time, based on pooled pain assessments from the
17 five trials. This exploration suggests that the
18 analgesic effect of extended-release
19 SABER-bupivacaine relative to immediate-release
20 bupivacaine HCl may have extended through 48 hours
21 after surgery.

22 Let me sum up the data in support of

1 efficacy. In the two pivotal trials, one a soft
2 tissue surgical model and one an orthopedic model,
3 statistically significant and clinically relevant,
4 reduction in pain was demonstrated compared with
5 placebo control and supported by postsurgical
6 reductions in opioid use, including delays in time
7 to first use.

8 Meta-analysis of all six adequate and
9 well-controlled trials indicated that
10 SABER-bupivacaine was superior to placebo for both
11 pain control and reduction of opioid use with 95
12 percent confidence intervals that did not span
13 unity. Improvements were seen across the entire
14 range of pain intensities, and the duration of
15 benefit lasted through 72 hours relative to
16 placebo.

17 Although there were no adequate data in our
18 clinical data set comparing SABER-bupivacaine with
19 bupivacaine HCl, a pair of exploratory
20 meta-analyses suggested improvement in 72-hour pain
21 control and an extended duration of analgesia
22 relative to the immediate-release product.

1 Now, let's examine the safety data
2 supporting the safety of SABER-bupivacaine. The
3 safety population for the clinical program as a
4 whole consisted of 1463 subjects divided among a
5 variety of treatment groups. The largest of these
6 were the SABER-bupivacaine 5 mL group in which 735
7 subjects were exposed to the proposed commercial
8 dose; the bupivacaine HCl group with 272 subjects;
9 and the SABER placebo; that is the SABER
10 formulation without active bupivacaine base
11 component. That group had 268 subjects.

12 Before presenting the results, I'd like to
13 spend a moment describing some issues pertinent to
14 the safety analysis. Because of the heterogeneity
15 of the trials in the clinical program, the task of
16 defining the safety profile of SABER-bupivacaine
17 required some care.

18 The chief issue was that depending on the
19 particular trial, various symptoms may have been
20 reported spontaneously by the subjects in response
21 to open-ended questions such as have you had any
22 bothersome symptoms today, or may have been

1 reported in response to specific queries like have
2 you felt drowsy today?

3 As is well known to clinical researchers,
4 solicited symptoms of the latter type are reported
5 with far higher frequency than those that rely on
6 the subject's spontaneous recollections. For this
7 reason, it was imperative, when handling such
8 adverse event reports, not to commingle the two
9 types; otherwise, confounding could occur that
10 would make one or another adverse event appear
11 imbalanced between treatment groups when in fact
12 there was no such imbalance.

13 Avoiding such false positives, several of
14 which were present in the original 2013 submission,
15 was one of the important purposes of reanalyzing
16 the full data set for our 2019 complete response
17 submission. To obtain the most accurate and
18 informative picture of SABER-bupivacaine's safety,
19 we undertook an exhaustive review of the pertinent
20 data in our safety data set.

21 Since receiving the 2014 complete response
22 letter, we also conducted an entirely new trial

1 called PERSIST in laparoscopic cholecystectomy,
2 specifically to examine by solicitation several
3 safety topics of special interest, the results of
4 which I'll outline for you shortly.

5 Since the new trial vastly expanded the pool
6 of subjects treated with a non-SABER or non-vehicle
7 control, primarily immediate-release bupivacaine
8 HCl, it was important to fold the results of the
9 new study into the aggregate safety analysis, which
10 we did in our 2019 ISS. This updated analysis, as
11 previously mentioned, is not included in the FDA
12 briefing book; only the ones from PERSIST itself
13 and the original 2013 submission.

14 Let's start with the SABER-bupivacaine
15 adverse events profile. There was a single death
16 in the entire clinical program, which both the
17 principal investigator and sponsor judged unrelated
18 to treatment with the study drug. Beyond that, the
19 frequency and distribution of serious
20 treatment-emergent adverse events appeared
21 unremarkable for this surgical population.

22 I'm going to show you a series of four

1 adverse event tables. These are sorted according
2 to control group, shown at the top of this 2-by-2
3 table, and the method by which the adverse events
4 were collected, shown on the left. In this way,
5 AEs collected in a similar manner from similar
6 trials will be compared with one another, thereby
7 avoiding the problem of confounding I described
8 earlier.

9 The information shown in these tables can
10 also be found in your briefing books, and we'll be
11 happy to discuss any questions you may have during
12 the Q&A session.

13 First up, spontaneously reported TEAEs in
14 all studies with SABER-bupivacaine HCl treatment
15 arms. In this comparison, the most prominent
16 difference between SABER-bupivacaine and
17 bupivacaine HCl was bruise-like discoloration at
18 the surgical site, which the Medical Dictionary for
19 Regulatory Activities, or MedDRA, translates into
20 the term post-procedural contusion.

21 This AE was reported more frequently in the
22 SABER-bupivacaine group than the plain bupivacaine

1 group. I'll go into more detail on bruise-like
2 discoloration in a couple of minutes. Other than
3 that, a clinically meaningful pattern of
4 differences between the two groups did not emerge
5 in this comparison.

6 Next, TEAEs that were specifically queried
7 or solicited in trials that had bupivacaine HCl
8 arms. Here, the incidence of all symptoms were
9 lower in the SABER-bupivacaine than the bupivacaine
10 HCl group. TEAEs that were spontaneously reported
11 in placebo-controlled trials show only small
12 sporadic differences between groups. Finally,
13 TEAEs that were specifically queried or solicited
14 in placebo-controlled studies show almost no
15 differences between groups.

16 Now, I'd like to turn to some topics of
17 special interest. These are areas that have either
18 come up in the 2014 complete response letter at
19 various points in our other interactions with the
20 FDA or would otherwise be of interest. First, you
21 might wonder whether the 660 milligrams of
22 bupivacaine contained in the single dose of

1 SABER-bupivacaine presents a risk of local
2 anesthetic systemic toxicity or LAST. Let me walk
3 you through the reasons why we think this is not a
4 concern.

5 As you've seen, the SABER-bupivacaine
6 formulation was developed to provide slow, stable
7 release of bupivacaine over approximately 72 hours.
8 Consistent with this goal, the product's PK profile
9 varies in the time-to-peak plasma concentration,
10 but very little in the maximum concentration. And
11 as mentioned earlier, the risk of inadvertent,
12 intravascular injection, an important cause of
13 overdose, with infiltrated bupivacaine HCl is low,
14 owing to the fact that a needle is not typically
15 used for administration.

16 On the left of this slide is a plot of the
17 distribution of maximum plasma concentration seen
18 in every subject in the clinical program who was
19 exposed to SABER-bupivacaine. The highest C_{max}
20 observed was 2850 nanograms per mL in a single
21 subject undergoing laparoscopically assisted
22 colectomy, which fell short of the point at which

1 the risk of LAST begins to increase.

2 On the right is a plot of the distribution
3 of maximum plasma concentrations seen in a
4 systematic review of the literature on bupivacaine
5 HCl pharmacokinetics, showing that Cmax values into
6 the several thousands occurred commonly in clinical
7 practice and also in the absence of reported toxic
8 events.

9 In its most recent practice advisory
10 published in 2017, the American Society of Regional
11 Anesthesia and Pain Medicine cataloged several
12 hundred recent cases of LAST, and noted that the
13 most serious presenting symptoms related to either
14 the central nervous system or the cardiovascular
15 system.

16 This slide shows the most common CNS
17 presentations of LAST. In the SABER-bupivacaine
18 clinical program, these events were either not
19 seen, occurred with equal frequency in the
20 SABER-bupivacaine and placebo groups, or as in the
21 single case of unconsciousness, were clearly
22 unrelated to LAST.

1 In the newly conducted PERSIST trial,
2 scheduled inquiries about the presence or absence
3 of 10 symptoms of interest, including the six shown
4 here, that could potentially be related to LAST
5 were made over the first 3 days of the trial. And
6 as a reminder, PERSIST was divided into Part 1,
7 which was saline placebo controlled, and Part 2,
8 which is bupivacaine HCl controlled.

9 The comparative incidence of these six
10 symptoms is shown on the left for Part 1 and on the
11 right for Part 2. No clinically meaningful pattern
12 of differences in the incidence of these symptoms
13 between SABER-bupivacaine, represented by the blue
14 bars in both graphs, in either of the control
15 groups can be discerned.

16 This slide presents the comparative
17 incidence of the same six symptoms for all the
18 trials in the clinical program that included a
19 bupivacaine HCl arm. The graph on the left shows
20 the incidence in cases where the symptoms were
21 solicited via questionnaire, and the graph on the
22 right shows the incidence of these symptoms as

1 reported spontaneously. Other than the fact that
2 the symptoms were seemed to occur more frequently
3 when solicited, as one would expect, no clinically
4 meaningful pattern of differences between the two
5 treatment groups is evident.

6 Now, before we go on, I'd like to stop for a
7 second and mention our 2013 ISS on which the
8 clinical and statistical reviews in your FDA
9 briefing books are largely based. As you can see
10 here, when the FDA reviewed our original ISS, it
11 was correct in stating that there was an imbalance
12 of neurologically-related adverse events when
13 SABER-bupivacaine was compared with bupivacaine
14 HCl.

15 As I alluded to earlier, this was an
16 unfortunate result of confounding between solicited
17 adverse events and the adverse events that were
18 spontaneously reported. The relatively small
19 number of subjects in the bupivacaine HCl group was
20 also pointed out by FDA reviewers and was the
21 impetus for their request for a new trial using a
22 non-SABER containing control.

1 In subsequent communications, the FDA
2 invited us to re-analyze the adverse event data to
3 support our contention that these imbalances were
4 artifactual. We did so, folding in the new data
5 from the PERSIST study, which added 148 bupivacaine
6 HCl subjects to the safety data set, more than
7 doubling it.

8 Now, here's what happens when these 10
9 events of interest are appropriately separated
10 according to the mode of collection. The incidence
11 of solicited AEs on the left is now greater across
12 the board in the bupivacaine HCl group than the
13 SABER-bupivacaine group, and the incidence of
14 spontaneously reported AEs on the right is
15 comparable between the two groups. These updated
16 analyses were included in our 2019 ISS and are
17 available in our briefing book, but are not present
18 in the FDA's briefing book.

19 As I've shown, any conclusions drawn from
20 the FDA's 2013 medical and statistical reviews must
21 be carefully considered to determine whether they
22 represent the most accurate and up to date

1 characterizations of the SABER-bupivacaine safety
2 profile.

3 Now, let's move on. This slide shows the
4 most common cardiovascular presentations of LAST
5 according to the ASRA practice advisory. In the
6 SABER-bupivacaine clinical program, these events
7 either were not observed, did not vary between
8 treatment groups, or were not correlated with
9 elevated bupivacaine plasma levels.

10 The next several slides compared the
11 placebo-corrected change from baseline of several
12 measures of cardiac conduction that could be
13 affected by LAST with the bupivacaine plasma
14 concentration as it evolved over time, after
15 SABER-bupivacaine administration.

16 In this graph, we see that the PR interval,
17 the solid blue line, did not vary with the rise and
18 fall over 72 hours of the plasma bupivacaine
19 concentration, the dotted red line, indicating that
20 the two were not correlated; same picture for the
21 QRS interval, same picture for the QT interval, and
22 finally, same picture for the heart rate, no

1 correlation with plasma bupivacaine concentration.

2 123 subjects treated with SABER-bupivacaine
3 and 75 treated with SABER placebo underwent Holter
4 monitoring for 72 hours after surgery. The Holter
5 report turned up no evidence of heart rate changes
6 or supraventricular arrhythmias correlated with
7 bupivacaine concentration, and no evidence that
8 ventricular arrhythmias or proarrhythmic events
9 varied by treatment group. To wrap up, we conclude
10 that the risk of LAST with SABER-bupivacaine
11 treatment is no greater than that associated with
12 the immediate-release bupivacaine, and possibly
13 lower.

14 Next topic, does the benzyl alcohol
15 component of SABER-bupivacaine cause adverse
16 effects? As a reminder, benzyl alcohol is an
17 excipient found in numerous drug and cosmetic
18 products, including those approved for parenteral
19 use in both adults and children.

20 Benzyl alcohol pharmacokinetics were
21 characterized in the abdominal hysterectomy study.
22 The plasma concentration was highest at the initial

1 one hour blood draw, diminished by a factor of 10
2 at 8 hours and became undetectable by 24 hours.
3 Although the true Cmax was not captured, it was
4 estimated to be a little over 0.6 milligrams per
5 liter at 23 minutes.

6 For context, these plasma concentrations
7 fell well within the asymptomatic range based on
8 both animal studies and on the reported plasma
9 concentrations of benzyl alcohol containing drugs
10 previously approved for use. Notably, a topical
11 lice treatment called Ulesfia, indicated for
12 children as young as 6 months of age, produced peak
13 plasma concentrations of up to 3 milligrams per
14 liter or somewhere between 3 and 5 times the level
15 of SABER-bupivacaine with no reports of
16 neurologically-related adverse events noted in the
17 product label.

18 In a written communication, FDA had
19 questioned whether the effects of systemic benzyl
20 alcohol could cause a delay in discharge from the
21 post-anesthesia care unit, or PACU, following
22 surgery. For that reason, both the time to

1 discharge eligibility assessed at 15-minute
2 intervals by the standardized mPADSS scoring system
3 and the actual time to PACU discharge were measured
4 in the newly conducted PERSIST study. The results
5 showed no differences between treatment groups,
6 indicating that systemically-absorbed benzyl
7 alcohol from SABER-bupivacaine did not affect
8 immediate postoperative recovery.

9 By FDA request, vital signs and oxygen
10 saturation were also monitored at 15-minute
11 intervals for a minimum of 2 hours after surgery in
12 the PERSIST trial to determine whether they were
13 affected by benzyl alcohol. No differences were
14 seen among the three treatment groups in the
15 postsurgical change from baseline in any of these
16 parameters.

17 Time to ambulation after surgery in the
18 PACU, which might have been delayed if benzyl
19 alcohol were causing untoward CNS effects, revealed
20 no meaningful difference between treatment groups.
21 And finally, when subjects were specifically
22 queried about 10 symptoms of interest to the FDA in

1 the newly conducted PERSIST study, no meaningful
2 differences between treatment groups, with the
3 possible exception of drowsiness, were observed at
4 the 6-hour mark when the effects of benzyl alcohol,
5 if any, might be felt.

6 Since, as shown in the previous slides,
7 there were no concomitant changes in vital signs or
8 blood oxygenation, no delays in PACU discharge or
9 time to ambulation, all objective clinical
10 outcomes, it would appear that any differences in
11 the subjective symptomatology seen in these graphs
12 were inconsequential from a clinical standpoint.

13 Now, before we leave this slide, I'd like to
14 address a point made by the division in its
15 briefing document regarding neurologically-related
16 adverse events and benzyl alcohol exposure. These
17 graphs depict the identical data shown to you in
18 tabular form in the FDA briefing book, with the
19 exception that the table contains an additional
20 decimal place worth of precision like this.

21 The FDA notes that the incidence of
22 drowsiness, which was the actual solicited symptom,

1 metallic taste or dysgeusia, headache, and itching
2 or pruritus were elevated among subjects treated
3 with SABER-bupivacaine. It then goes on to state
4 that, quote, "Because somnolence, headache,
5 dysgeusia, and pruritis were observed with greater
6 frequency in SABER-treated patients in the clinical
7 studies evaluated during the original NDA review,
8 it is very likely that systemic BA may be the
9 cause," unquote.

10 I'd like to spend a minute explaining why
11 the evidence supporting this assertion is weak.
12 First, the imbalances observed in the original 2013
13 NDA review were a result of confounding between
14 solicited and non solicited adverse events, as I've
15 just demonstrated, and thus were purely
16 artifactual.

17 Second, the statement that subjects treated
18 with SABER-bupivacaine had an increased incidence
19 of these four symptoms during the first 6 hours
20 after surgery in PERSIST, while true, technically
21 is misleading; for example, pruritis, 2.1 versus
22 2.2 on the left and 3.4 versus 4.1 on the right.

1 These differences are not particularly impressive.
2 Headache gives you a similar picture, as does
3 metallic taste or dysgeusia. As a clinician, I'd
4 be hard-pressed to call these differences
5 clinically meaningful.

6 Now, let's take a look at drowsiness, which
7 is the only one of these four symptoms one might
8 plausibly argue was elevated in the
9 SABER-bupivacaine group in more than a marginal
10 fashion, however, let's also take a look at nausea
11 and vomiting. Nausea was reduced in the
12 SABER-bupivacaine subjects by about the same 6 to
13 8 percent margin that drowsiness was increased. I
14 don't think these data have been clearly
15 communicated in the FDA's briefing.

16 Frankly, I suspect that most patients would
17 prefer to be drowsy after surgery than nauseated.
18 I might even propose that the small increase in
19 postoperative drowsiness reported by the
20 SABER-bupivacaine group was not a benzyl alcohol
21 effect at all, but actually a result of increased
22 comfort. We conclude that the adverse effects of

1 benzyl alcohol have not been detected in trials of
2 SABER-bupivacaine. Increased postoperative
3 drowsiness was balanced by a decrease in nausea and
4 vomiting.

5 Next topic, does the SAIB component of
6 SABER-bupivacaine cause adverse effects? The
7 result of animal studies showed some long-term
8 localized persistence of SAIB after high-dose
9 subcutaneous injection into rabbits, and also
10 showed some foreign body reactions in rats of a
11 type common to depot formulations.

12 Note that the dose per rabbit on a
13 weight-adjusted basis was equivalent to a human
14 dose of more than 50 mL or 10 times the actual
15 recommended human dose, and it was restricted to a
16 small quiescent subcutaneous space rather than
17 being spread throughout a larger volume incisional
18 space that is vascularized and actively healing.
19 Clinical studies have not replicated these animal
20 findings in humans.

21 MRIs obtained 6 months after abdominal
22 hysterectomy did not show evidence of retained SAIB

1 at the incision site, nor did they show other local
2 tissue abnormalities such as fibrosis. MRIs
3 obtained 6 and 18 months after shoulder arthroscopy
4 were also negative for tissue abnormalities or
5 evidence of retained SAIB.

6 Physical examination of the surgical site, 3
7 and 6 months after inguinal hernia repair and
8 6 months after hysterectomy, detected no healing
9 abnormalities, and histologic examination of
10 peri-incisional cutaneous tissue during the acute
11 phase of healing found no unexpected pathology.

12 Just as a reminder by the way, when used in
13 abdominal surgery, SABER-bupivacaine is
14 administered superficial to or outside the fascial
15 tissue layer after it has been closed with sutures
16 and not into the abdominal cavity itself. Thus,
17 any theoretical concerns about SAIB-induced
18 fibrosis would apply only to the skin and soft
19 tissues at the surgical site, which we have
20 carefully investigated and ruled out, and could not
21 be associated with adhesions of the internal
22 organs, which are not exposed to the study drug.

1 Based on the failure to replicate findings
2 from animal studies in human subjects, we conclude
3 that the SAIB component of SABER-bupivacaine does
4 not cause long-term adverse effects at the surgical
5 site.

6 Next, given that SABER-bupivacaine is
7 administered directly into the surgical incision,
8 is there any evidence that it impairs wound
9 healing? During the acute recovery period, it was
10 important to establish the incidence of three
11 potentially serious postsurgical complications,
12 dehiscence, hematoma, and infection, relative to a
13 non-SABER containing control. Bruise-like
14 discoloration, or post-procedural contusion as it
15 was described earlier, was also of interest,
16 although less concerning from a clinical
17 standpoint. Testing for appropriate long-term
18 healing at the surgical site was also a priority.

19 To meet these objectives, we carefully
20 reviewed our existing data, added new data from the
21 PERSIST trial, and reported the results in our
22 updated 2019 ISS. Now let's examine these

1 potential complications one at a time.

2 Twenty-four subjects had some degree of
3 separation of the wound margins. Of these, 22 had
4 superficial dehiscence involving only the cutaneous
5 layer and 2 had fascial dehiscence. While the
6 majority of dehiscences, if treated at all,
7 required only local wound care, 3 cases were
8 clinically important in that they required surgical
9 intervention. Two of these cases were in the
10 SABER-bupivacaine group and one was in the SABER
11 placebo group. All three of these subjects had
12 significant underlying risk factors for dehiscence.

13 Although no cases of clinically relevant
14 dehiscence were reported in the bupivacaine group
15 or the saline placebo groups, these groups were
16 substantially smaller than the SABER-bupivacaine
17 group. Looking at the upper bounds of the 95
18 percent confidence intervals for all the groups, it
19 is evident there were no important differences
20 between any of the groups.

21 Here's a representative selection of
22 published dehiscence rates, superficial dehiscence

1 on the left and fascial dehiscence on the right.
2 Here are the rates seen in trials of
3 SABER-bupivacaine. The incidence of both,
4 superficial and fascial dehiscence, is considerably
5 higher in clinical practice than was seen in the
6 SABER-bupivacaine clinical studies, suggesting that
7 none of the treatment groups produced a dehiscence
8 signal exceeding expected limits.

9 In the PERSIST study, in laparoscopic
10 cholecystectomy, which carefully evaluated
11 dehiscence among other wound-related complications,
12 dehiscence rates were low and comparable between
13 treatment groups. Although the incisions were
14 genuinely small, the relative quantity of
15 SABER-bupivacaine instilled into each incision was
16 large, meaning that if SABER-bupivacaine had a
17 detrimental effect on wound repair, it should have
18 been apparent.

19 In vitro studies have established that
20 SABER-bupivacaine did not reduce the tensile
21 strength or otherwise degrade the performance of
22 these common suture materials. Animal studies

1 assessing wound strength 7 days after treatment
2 with SABER-bupivacaine, vehicle control, or no drug
3 showed no difference in wound integrity between the
4 three groups.

5 A hematoma is a collection of blood or clot
6 at or near the incision caused by imperfect
7 hemostasis. Hematomas often resorb on their own
8 without intervention, but some are sufficiently
9 symptomatic or otherwise concerning as to require
10 drainage. Thirty-one hematomas were reported by
11 investigators among all clinical trial subjects,
12 but only 8 of these required drainage.

13 Although there was a slightly higher
14 incidence of hematomas overall among
15 SABER-bupivacaine treated subjects, the incidence
16 of clinically relevant hematomas, that is those
17 requiring drainage, was comparable between groups,
18 and in fact, the point estimate was slightly lower
19 among SABER-bupivacaine treated subjects than
20 bupivacaine HCl treated subjects. Published
21 hematoma rates, shown in the lower half of the
22 slide, were higher than those seen in

1 SABER-bupivacaine in clinical trials.

2 Given that bupivacaine itself is not
3 suspected to increase infection rates, a reasonable
4 question to ask is whether the SABER formulation
5 could be responsible for increasing the risk of
6 postoperative infection. To address that question,
7 we compared infection rates for SABER-bupivacaine
8 with those of non-SABER controls.

9 There were six trials with non-vehicle
10 comparison arms, 5 that used bupivacaine HCl and 1
11 that used saline placebo. This slide presents the
12 incidence of surgical site infection for these two
13 groups. There were no important differences
14 between comparators. Most infections were treated
15 with antibiotics and local wound care.

16 No subjects returned to the operating room
17 for surgical intervention, and there was a single
18 SAE report in the SABER-bupivacaine group of a post
19 laparotomy subject requiring prolonged
20 hospitalization for drainage and antibiotic
21 therapy. Apart from this one subject with a severe
22 infection, all other infections were considered

1 mild or moderate in severity.

2 Since published infection rates show a clear
3 distinction between long incisions, which have
4 higher infection rates, and shorter endoscopic
5 incisions, which have lower rates, we prepared a
6 table of infection rates for two representative
7 surgical models from our clinical program with long
8 and short incisions, laparotomy and laparoscopic
9 cholecystectomy, both of which had non-vehicle
10 comparison arms.

11 There were no important differences between
12 the SABER-bupivacaine and bupivacaine HCl infection
13 rates for both long and short incisions, and the
14 incidence of infection was similar to published
15 rates for the respective procedure types. Based on
16 these data, the SABER formulation does not appear
17 to be associated with a substantive safety signal
18 for surgical site infection.

19 Now, let's discuss bruise-like
20 discoloration. Post-surgical bruising typically
21 results from a combination of surgical trauma to
22 the capillary bed and the subcutaneous spread of

1 blood and is often tender to the touch. The
2 bruise-like discoloration we have observed in
3 association with SABER-bupivacaine appears
4 dissimilar in that tissue trauma appears to play a
5 minimal role and the area of discoloration is not
6 painful or tender to palpation. We suspect the
7 ideology to be bupivacaine-induced vasodilation
8 followed by transport of red blood cells and red
9 blood cell components into the surrounding
10 subcutaneous tissue by benzyl alcohol.

11 The discoloration has been more pronounced
12 with larger open incisions in areas with loose
13 subcutaneous tissues such as the abdomen, and by
14 contrast was not seen at all after shoulder
15 arthroscopy. Signs of inflammation such as
16 swelling, tenderness, and warmth have not been
17 observed, and the discolored area is non-blanching
18 to finger pressure.

19 Like a typical bruise, the discoloration
20 fades over a 2-to-4 week period with a series of
21 color changes and no clinical sequelae.
22 Bruise-like discoloration has been observed to

1 cover a wider area than typical postsurgical
2 bruises, which we believe to be an effect of the
3 benzyl alcohol mediated transport.

4 Data from the PERSIST study in laparoscopic
5 cholecystectomy have helped create a more detailed
6 picture of this phenomenon. Bruise-like
7 discoloration was more prevalent among subjects
8 treated with SABER-bupivacaine than with non-SABER
9 comparators, but even in the saline placebo group,
10 bruising reached 50 percent.

11 Discoloration was not mistaken for infection
12 or hematoma because its onset was comparatively
13 early and it exhibited none of the cardinal signs
14 of inflammation. Reports of bruise-like
15 discoloration peaked on study day 4 and diminished
16 over a matter of weeks. Discoloration was fully
17 resolved in all but a handful of cases by day 30.

18 In 803-027, which was an open-label study of
19 10 subjects undergoing major long-incision
20 abdominal surgery, the investigator lightly
21 palpated the area of most severe discoloration, and
22 just prior to that recorded each subject's baseline

1 pain. Most subjects reported no tenderness in
2 response to palpation. Those who did had pain on
3 palpation that exactly matched their baseline
4 scores, indicating that the discoloration was
5 non-tender.

6 Long-term healing of the surgical incision
7 was assessed in several studies as summarized here.
8 With minor exceptions considered unrelated to the
9 study drug, all wounds healed as expected and no
10 signs of tissue abnormalities were detected at
11 long-term follow-up.

12 Both the newly conducted PERSIST study and
13 the full safety database presented in the 2019 ISS
14 demonstrated no excess risk of clinically important
15 wound-related complications with SABER-bupivacaine
16 treatment. Bruise-like discoloration was observed
17 more frequently, although it appeared clinically
18 inconsequential, resolving without intervention or
19 sequelae.

20 Next and final question, is there a risk
21 that SABER-bupivacaine could cause chondrolysis or
22 other shoulder-related complications if instilled

1 subacromially? For those of you unfamiliar with
2 chondrolysis, this is a name given to the nearly
3 complete loss of articular cartilage associated
4 with the infusion of concentrated bupivacaine into
5 the joint space at high flow rates over a period of
6 days after surgery. The effects are typically
7 evident within 6 months after the initial insult.
8 Studies indicate that transient bupivacaine
9 exposure on the other hand does not cause
10 chondrolysis, nor does the infusion of bupivacaine
11 into the subacromial space, which is where
12 SABER-bupivacaine was placed in our shoulder
13 arthroscopy studies.

14 Let me briefly summarize what we did to
15 ensure that chondrolysis had not occurred with
16 exposure to SABER-bupivacaine. In two studies that
17 had long-term follow-up components, baseline and 6
18 or 18 month MRIs, respectively, were centrally read
19 by experienced musculoskeletal radiologists in a
20 blinded fashion, who determined that there was no
21 evidence in any subject of chondrolysis or other
22 unexpected abnormalities of the shoulder joint or

1 surrounding tissues.

2 In the third study, which had no MRI imaging
3 or formal long-term follow-up, neither a phone
4 survey of the principal investigators at 7 years
5 post-surgery nor written survey at 10 years turned
6 up any reports of chondrolysis among the PERSIST
7 participants. Based on evidence collected from the
8 three shoulder arthroscopy trials, we conclude that
9 concerns regarding chondrolysis or other
10 shoulder-related complications are unwarranted.

11 Now, I'd like to sum up the safety findings
12 for SABER-bupivacaine. Based on newly collected
13 data from the PERSIST trial, as well as careful
14 analysis of the entire safety data set, as shown in
15 the 2019 ISS, the adverse event profile for
16 SABER-bupivacaine appears unremarkable, with the
17 exception of an elevated incidence of bruise-like
18 discoloration.

19 Several topics of special interest,
20 including the risk of local anesthetic systemic
21 toxicity, the potential for benzyl alcohol
22 intoxication, and the possibility of long-term

1 SAIB, have been closely examined and have not been
2 shown to present a meaningful safety signal, based
3 on detailed and comprehensive data from the
4 complete clinical data set.

5 Likewise, the risks of wound-related
6 complications and chondrolysis also appear to be
7 low. Thus, the overall safety profile of
8 SABER-bupivacaine appears comparable to that of the
9 reference drug, immediate-release bupivacaine HCl,
10 which has a long-standing history of use in the
11 perioperative setting.

12 Now, I'd like to summarize our view of the
13 clinical relevance of our findings. We believe the
14 positive efficacy outcomes presented to you here
15 are clinically relevant in a postsurgical setting.
16 We base this on the results of our two replicative
17 efficacy trials, one in a soft tissue model and one
18 in an orthopedic or bony model; the collective
19 evidence of efficacy developed from meta-analyses;
20 supportive reductions in several measures of opioid
21 use; and data favoring increased duration of
22 analgesia compared with placebo. Improvements

1 relative to the immediate-release product have also
2 been suggested.

3 Safety data have been developed for more
4 than 800 adult subjects dosed with
5 SABER-bupivacaine during the course of the clinical
6 program. In direct comparisons, the safety profile
7 of SABER-bupivacaine has been shown to be
8 comparable with that of bupivacaine HCl. Issues of
9 potential concern have been carefully investigated,
10 and related safety signals of importance have not
11 been uncovered.

12 A heterogeneous surgical population was
13 studied during the SABER-bupivacaine development
14 program with no important safety or efficacy
15 differences turning up between subpopulations.
16 SABER-bupivacaine was studied in an extensive and
17 diverse clinical program involving a multitude of
18 surgical procedures of various types and levels of
19 invasiveness, and the resulting safety profile has
20 been consistent and acceptable across surgical
21 models.

22 At the beginning of our presentation, we

1 offered you a preview of our conclusions. In
2 support of those conclusions, we now have shown you
3 evidence of efficacy derived from our adequate and
4 well-controlled trials and evidence of safety
5 derived from targeted investigations in the PERSIST
6 trial, and a comprehensive analysis of our current
7 safety database as presented in our updated 2019
8 Integrated Summary of Safety. As such, we now
9 believe an appropriate risk-benefit assessment can
10 be performed supporting the approval of
11 SABER-bupivacaine.

12 Now to be clear, we don't claim that this
13 drug eliminates postoperative pain. The data show
14 that SABER-bupivacaine provides a meaningful
15 incremental reduction in pain intensity that should
16 be additive with that of other agents and
17 techniques to provide improved postoperative pain
18 control. This is the direction in which acute pain
19 management is rapidly moving, and we view the
20 addition of a low risk, non-opioid local analgesic
21 such as SABER-bupivacaine to the multimodal toolbox
22 as a clear win for patients and clinicians alike.

1 Now, I'd like to introduce two clinicians,
2 the first, a general surgeon, and the second, an
3 anesthesiologist, both of whom have had firsthand
4 experience using this drug in clinical trials, to
5 present their perspectives on SABER-bupivacaine,
6 and I'll start with Dr. Asok Doraiswamy.

7 **Applicant Presentation - Asok Doraiswamy**

8 DR. DORAISWAMY: Good morning, everybody.
9 My name is Asok Doraiswamy. I'm a general surgeon
10 from Pasadena, California. I'd like to disclose
11 that I have received consulting fees from DURECT,
12 and I've received compensation for travel and hotel
13 expenses.

14 I'm here to give you a general surgeon's
15 perspective on SABER-bupivacaine. I've been a
16 principal investigator on two trials, where I
17 performed laparoscopic cholecystectomies. I've
18 administered SABER-bupivacaine to 43 of my
19 patients, so I'd like to briefly discuss my
20 experience and what I see as distinct advantages of
21 this drug.

22 First, the method of administration is a

1 clear advantage. A needle-free administration is
2 safer for the patient, surgeon, and surgical team.
3 From my perspective, the risk of intravascular
4 administration drops to zero. This is a very rare
5 complication but can have catastrophic and
6 potentially irreversible neurologic and cardiac
7 toxicity. The risk of needle stick injury also
8 drops to zero for surgeon and surgical team
9 members.

10 In addition, direct application takes a
11 fraction of the time compared to an infiltrative
12 technique. My clinical experience and review of
13 the data give me confidence that this drug would be
14 a benefit to my patients without posing any greater
15 risk than bupivacaine.

16 The bruising that was discussed earlier was
17 not a clinical concern in my patients. We did
18 indeed note a higher incidence of bruising in
19 patients that received SABER-bupivacaine, but not
20 one of the 43 patients that received study drug
21 during the course of the studies called me to
22 complain about the appearance of their wounds or

1 any bruising.

2 Similarly, not a single patient in the
3 bupivacaine arms of the study called me to complain
4 about the appearance of their wounds. This is
5 because patients understand that when tissues are
6 cut, there's a chance that bruising may occur, but
7 at no time was bruising confused for cellulitis or
8 hematoma. Cardinal signs of infection such as
9 blanching, warmth, or increased pain were all
10 absent. The resolution of bruising was identical
11 to bruises that are seen with other incisions and
12 that discoloration was completely resolved by about
13 one month.

14 I think that one of the most important
15 applications for SABER-bupivacaine would be in the
16 outpatient setting. As a general surgeon, I
17 perform a lot of hernia repairs, cholecystectomies,
18 and other procedures where patients are discharged
19 within a couple of hours of surgery. Having
20 SABER-bupivacaine on board would make me feel more
21 comfortable sending patients home with fewer
22 opioids than I currently prescribe.

1 Overall, I think that SABER-bupivacaine
2 would be seriously considered by surgeons of
3 multiple specialties for the reasons that I've
4 listed: ease of use; a safer application
5 technique; opioid-sparing properties compared to
6 traditional bupivacaine; and a trend towards
7 improved analgesia over 72 hours. I feel that
8 SABER-bupivacaine would be an excellent and unique
9 addition to our currently available multimodal
10 treatment options for acute postoperative pain.
11 Thank you.

12 **Applicant Presentation - Harold Minkowitz**

13 DR. MINKOWITZ: Good morning. My name is
14 Dr. Harold Minkowitz. I've been a clinical
15 researcher with DURECT, and their response to the
16 conduct of the clinical trials with me. I've also
17 acted as a paid consultant for DURECT, and they
18 have reimbursed my travel and other related
19 expenses.

20 As anesthesiologists, we are often called
21 upon to consult and advise upon acute pain
22 management after surgery. As my colleagues Dr. Gan

1 and Dr. Doraiswamy have discussed, physicians are
2 doing all we can to reduce our reliance on opioids
3 to treat acute postoperative pain. We are also
4 embracing the philosophy of enhanced recovery after
5 surgery in order to decrease our reliance on
6 opioids and to allow patients to return to baseline
7 function as soon as possible after surgery.

8 I have served as an investigator on a number
9 of trials in a technical development program for
10 this agent, and I have also reviewed the data. As
11 such, I'm comfortable with the safety and efficacy
12 profile of SABER-bupivacaine. SABER-bupivacaine
13 was specifically designed to be a long-acting local
14 anesthetic for postoperative pain control. It fits
15 precisely within the current guidelines for
16 postoperative pain management, and if approved
17 could be an important addition to our analgesic
18 tool set. I thank you for your time.

19 **Clarifying Questions**

20 DR. LITMAN: Thank you. We will now proceed
21 to the portion of the meeting that deals with
22 clarifying questions for DURECT. Please remember

1 to state your name for the record before you speak,
2 and if you can, please direct questions to a
3 specific presenter. We're allotted 15 minutes for
4 these clarifying questions. I understand that may
5 not be enough this morning, so if possible, please
6 make your questions as specifically clarifying as
7 possible. Again, if you want to be called on, just
8 turn your name tag up like this.

9 Dr. Zacharoff?

10 DR. ZACHAROFF: Hi. Kevin Zacharoff, and my
11 questions would be for Dr. Verity. With respect to
12 the post-procedural contusion, was there any
13 identification placed on patients to alert the
14 staff that the patient had received the study
15 medication so they could understand that the
16 bruising was related to the study drug
17 administration?

18 DR. VERITY: No. All the assessment of
19 bruises and everything, including pain
20 measurements, were done in a blinded fashion, so
21 there's no notification or label stuck on an
22 individual patient.

1 DR. ZACHAROFF: Thank you. One last quick
2 question. With respect to the incidence of the
3 adverse event of drowsiness, was there any
4 breakdown in data with respect to what the
5 anesthetic technique was for the patients who
6 experienced drowsiness?

7 Obviously, for the laparoscopic
8 cholecystectomy, general anesthetic would have been
9 the case, but in other situations, there might have
10 been patients who experienced drowsiness who had
11 regional anesthetics or local anesthetics like for
12 an inguinal hernia versus general anesthetic, and
13 I'm wondering if there's any breakdown with respect
14 to anesthetics.

15 DR. VERITY: With regard to the use of local
16 anesthetics, most, if not all, of our surgeries
17 were done under general anesthesia, except for one
18 trial that was done under local. That is not
19 included.

20 DR. ZACHAROFF: Okay. Thank you.

21 DR. LITMAN: Dr. Zaafran?

22 DR. ZAAFRAN: Thanks. Sherif Zaafran. This

1 is, I think, also directed to Dr. Verity. On
2 slide 46, I'm kind of interested as to what your
3 thoughts are as to why bupivacaine, which is short
4 acting -- and I'm presuming the only difference
5 between the two is that one just lasts longer and
6 the other one is a shorter-acting one; why there
7 was a pronounced decrease in pain scores with the
8 SABER-bupivacaine compared to bupivacaine.

9 This is I guess only specifically to
10 subacromial decompression surgery. It wasn't tried
11 with inguinal hernias or any of the other stuff,
12 was it?

13 DR. VERITY: I think to best answer your
14 question, I'd like to bring up Dr. Meisner, who
15 actually presented the slide, if I could afford to
16 do that.

17 DR. MEISNER: Thanks for the question. Just
18 to clarify, you're wondering about the early
19 improvement in pain with SABER-bupivacaine related
20 to bupivacaine HCl. Is that --

21 DR. ZAAFRAN: Well, I'm wondering why
22 there's a more

1 pronounced, according to the slide, pain relief
2 with SABER-bupivacaine compared to bupivacaine if
3 the properties of the drugs are supposed to be the
4 same, at least in the short term. And was this
5 only specifically related to subacromial
6 decompression or was there any comparison made to
7 more of a direct tissue type of application like
8 inguinal hernia or any of the other types of
9 surgery?

10 DR. MEISNER: Sure. There were only two
11 trials in our clinical trial experience that had
12 three arms that included SABER-bupivacaine, a
13 bupivacaine HCl comparator, and a placebo
14 comparator. One was the shoulder trial that you're
15 looking at, and the other was a hysterectomy trial,
16 which unfortunately demonstrated that there was no
17 assay sensitivity in that model whatsoever. So
18 this is the data that we have to go on.

19 Up, please. If you recall, we looked at the
20 release rate of bupivacaine from the
21 SABER-bupivacaine depot over time. If you notice,
22 we aimed for a target somewhere between 10 and

1 20 milligrams per hour, which is typically what one
2 would program into an infusion pump for a
3 continuous wound infusion. The gray shading, which
4 was a little more prominent on our projector, is
5 not coming out so well here, but you can see where
6 the brackets are, the infusion pump rate.

7 The thing to notice is that when first
8 instilled, the drug releases bupivacaine at a rate
9 closer to 20 milligrams per hour, and over time it
10 drops probably down to about 5. Our belief is that
11 in the early part of the postsurgical period, the
12 subjects are actually getting quite a bit more
13 bupivacaine, and toward the end of the 3 days,
14 they're getting somewhat less, which turns out to
15 be a perfect match to the evolution of postsurgical
16 pain over time, in which the initial hours are
17 where you really want the bupivacaine in place, and
18 by the end of 3 days, you're ready to trail off.

19 DR. ZAAFRAN: So with that exact same
20 slide -- again, that's 46 -- how does that explain
21 also that after 24 hours, there wasn't any
22 perceived difference between the SABER-bupivacaine

1 and bupivacaine as far as pain scores? And again,
2 this is the only one that I see as far as comparing
3 the two directly together, where it doesn't look
4 like there's a perceived difference when you go
5 into the 24 to 72 hours.

6 DR. MEISNER: Right. I have to remind you
7 that all the comparisons in our presentation with
8 immediate-release bupivacaine HCl were not powered
9 for efficacy. They were predesignated as
10 exploratory, so I don't really have the adequate
11 data to present you comparing our drug to plan
12 bupivacaine. This graph is presented for
13 transparency and completeness, and we can suggest
14 that there was some improvement through 12 to 24
15 hours, but we don't have the proper data in our
16 data set to answer your question.

17 DR. ZAAFRAN: Okay. The last question, I
18 think it's an important one for a lot of
19 anesthesiologists, were there any
20 studies -- because I didn't see it here -- that
21 mixed the two together, whether it be
22 SABER-bupivacaine and bupivacaine or

1 SABER-bupivacaine and other local anesthetics, and
2 are there any concerns about the two of them mixed
3 together causing any kind of issues?

4 DR. MEISNER: That's an interesting
5 question. It turns out that early on in our
6 development program, there were a total of -- I'm
7 sorry, I don't recall exactly, but it was something
8 like 70 or 80 or 90 subjects who got a mix of both
9 SABER-bupivacaine -- let's see if this slide does
10 it for me.

11 Up, please. This is a summary of some of
12 these early studies. At the time, we didn't know
13 how early the bupivacaine would be released out of
14 the depot, and there was a thought that maybe we
15 ought to co-administer plain bupivacaine in order
16 to get an earlier analgesic effect, and then the
17 depot would take over.

18 So what you can see from this slide is that
19 in some of these studies, people got quite a bit of
20 co-administered drug. In particular, if you look
21 at the hernia trial, in the two hernia trials, some
22 patients got 7 and a half mLs of SABER-bupivacaine,

1 which is greater than the dose we recommend for
2 clinical use, and on top of that, another 75
3 milligrams of plain bupivacaine. We've looked at
4 the safety data for these studies and, in fact, did
5 not see any effects of excess bupivacaine.

6 DR. LITMAN: Dr. McCann?

7 DR. McCANN: Mary Ellen McCann. This is for
8 Dr. Meisner as well --

9 DR. MEISNER: Sure.

10 DR. McCANN: -- I think slide 30. It's
11 about the issue of your post hoc analysis of the
12 preliminary data or the early data. Did the FDA
13 ask you to do that? Was that solicited by them for
14 you to do that?

15 DR. MEISNER: I just want to make sure I
16 understand your question completely before I answer
17 it.

18 DR. McCANN: Okay. Well, in general,
19 post hoc analyses are frowned upon --

20 DR. MEISNER: Sure.

21 DR. McCANN: -- and my understanding is the
22 FDA does not often accept them.

1 DR. MEISNER: Right.

2 DR. McCANN: But you did them, so I was
3 wondering whether there was an exception in this
4 case.

5 DR. MEISNER: Oh, sure. I just want to
6 completely understand which post hoc analysis you
7 were referring to.

8 DR. McCANN: In general, I thought all the
9 preliminary studies where you came up with a
10 hypothesis that was solicited versus non-solicited
11 adverse events.

12 DR. MEISNER: Let me offer an answer, and
13 you'll tell me if it satisfies your question. What
14 we did was we ran a series of trials, and we took
15 the trials as a collective and tried to present a
16 comprehensive safety picture, which is commonly
17 done. To that end, we grouped our safety events
18 into treatment groups, SABER-bupivacaine, placebo,
19 bupivacaine, et cetera, which would be a typical
20 way of presenting an overall safety profile in an
21 NDA submission.

22 We then sent that in to the FDA, noting the

1 fact that there was some confounding in this table,
2 which we felt created results that were not
3 accurate to what had actually happened, and in
4 fact, made a note in our original ISS that this had
5 occurred.

6 DR. McCANN: But you determined the
7 confounding post hoc, after you got the data, or
8 otherwise the data wouldn't have been confounded to
9 begin with, right?

10 DR. MEISNER: Well, all of the analyses that
11 go into building a comprehensive safety profile
12 are, in essence, post hoc. One can state safety
13 data for each trial individually, which one does in
14 the clinical study report, but when you aggregate
15 them together to try to create a full aggregate
16 safety profile, that's post hoc analysis, which is
17 what the FDA would typically expect to see in an
18 integrated summary of safety. So the confounding
19 was indeed post hoc, and the correction of the
20 confounding.

21 Our understanding that we really needed to
22 re-do these tables in order to present the most

1 accurate picture of safety was also, obviously, a
2 post hoc analysis, but it also included the safety
3 results from the entirely new PERSIST study, which
4 the FDA had specifically asked for because they had
5 told us, after the original submission, we didn't
6 have enough non-SABER comparators, and they wanted
7 a study with more SABER comparators in order to
8 explain that; and we took that study and integrated
9 it into the other safety data, which is what I
10 presented here.

11 DR. McCANN: Great. Thank you. I have
12 another slide, slide 94. I think you mentioned
13 that benzyl alcohol, the amount used is not
14 dangerous even in children. Any thought of
15 introducing this drug for children in the future?

16 DR. MEISNER: Pediatric studies are
17 typically done for approved drugs in a
18 postmarketing fashion, and that's something we
19 would certainly intend to do.

20 DR. McCANN: Then slide 115 about the
21 bruising. I know you did not find any color
22 changes, long-term color changes, but it's well

1 known with traumatic bruises that you can get
2 hemosiderin deposits that are permanent, and I
3 would imagine this might happen with this. Is that
4 going to be part of your labeling, do you think?

5 DR. MEISNER: That would be up to the FDA.
6 We did not, in any of our clinical trials, see any
7 long-term color changes on the skin area where the
8 bruises had been.

9 DR. McCANN: Thank you.

10 DR. LITMAN: In the interest of time, we're
11 going to do one more question by Dr. Higgins, but I
12 just want to remind everybody, please hold your
13 questions. I do anticipate a robust discussion at
14 some point today, and we should have time to do
15 that.

16 DR. HIGGINS: Jennifer Higgins. I have a
17 couple, and I'll try to keep them very brief. I
18 believe this is for Dr. Meisner, but perhaps
19 Dr. Verity. I'm interested in the 13 percent, as a
20 gerontologist, of the age group over 65, and some
21 up to the age of 87. I'm wondering -- and I didn't
22 see this, and I apologize if it's present and I

1 missed it -- how many older adults were in the bony
2 versus the soft tissue surgeries. As of slide 28,
3 how many were there in the 2 out of 5 not
4 well-controlled trials? Can you talk about any AEs
5 or experiences of older adults types of surgeries
6 and such?

7 DR. MEISNER: Sure. The vast majority of
8 older patients were in Study 803-025, Cohort 3,
9 which is the second bullet down under the support
10 of the studies on this slide. That was a trial of
11 laparoscopic-assisted colectomy. Most of these
12 older patients came in needing major
13 intra-abdominal surgery for various diagnoses,
14 cancer, diverticulitis, inflammatory bowel disease,
15 et cetera; so they were pretty much concentrated in
16 that particular surgery, that particular clinical
17 trial

18 Up, please. Here's a slide which shows you
19 actually what the distribution of older subjects
20 were in our clinical trials. I would say that in
21 terms of the orthopedic trials, there weren't a
22 tremendous amount of older subjects. Most of them,

1 as one might expect, showed up in the soft tissue
2 trials. Subacromial decompression to treat
3 impingement syndrome is typically in subjects, or
4 patients, between 40 and 60 years of old, 40 and
5 60 years of age.

6 DR. HIGGINS: So no pronounced AE
7 phenomenon.

8 What about slide 80? This may be
9 Dr. Meisner. The agitation in loss of
10 consciousness or vasovagal event, what were the
11 ages of those? And then more about those
12 experiences. I'm thinking about -- I know that you
13 said that total pain control is not the thrust and
14 use of this product, but I do wonder about
15 uncontrolled pain and breakthrough.

16 DR. MEISNER: Sure. The loss of
17 consciousness case, as I recall, was a relatively
18 young person I think in his 30's. This was
19 essentially a guy who had a laughing fit in his bed
20 and suddenly had a drop in his heart rate, which
21 obviously they put monitors on him, and it was
22 found to be sinus bradycardia, and he recovered

1 within about a minute back up to normal heart rate.
2 The investigator felt that it was simply a
3 vasovagal event and considered it unrelated to
4 bupivacaine exposure.

5 The agitation, I don't recall the age of
6 that subject. I'd be happy to find out and get
7 back to you.

8 DR. HIGGINS: That would be great, and one
9 last question about demographics. The fact that so
10 much of the study was done internationally and then
11 some discrepancy between a failed and successful
12 trial in the U.S. versus international, how did you
13 control for the variation in surgical experiences
14 and techniques internationally?

15 DR. MEISNER: Sure. In the case of all of
16 our clinical trials, we had a clinical operations
17 team who was responsible for traveling to
18 investigator sites and making sure that the various
19 investigators were appropriately trained. This was
20 especially true in our adequate and well-controlled
21 trials. In some of our early learning experiences,
22 things weren't as tightly controlled, but the ones

1 that are supplying efficacy data, we were well
2 assured that the surgical techniques were quite
3 similar between the U.S., the EU, and Australia,
4 and New Zealand, where most of those surgeries were
5 performed.

6 DR. LITMAN: Thanks. Let's take a break now
7 and reconvene with the FDA presentations at 10:15.
8 Panel members, please remember that there should be
9 no discussion of the meeting topic during the break
10 amongst yourselves or with any member of the
11 audience. Thank you.

12 (Whereupon, at 10:03 a.m., a recess was
13 taken.)

14 DR. LITMAN: It's 10:15, 10:16, so we're
15 going to proceed now with the FDA presentations.

16 **FDA Presentation - Renee Petit-Scott**

17 DR. PETIT-SCOTT: Good morning. My name is
18 Renee Petit-Scott. I'm the medical officer in the
19 Division of Anesthesiology, Addiction Medicine, and
20 Pain Medicine reviewing this application. I am
21 also a practicing board certified anesthesiologist.

22 An overview of the FDA presentation is

1 included here. I will begin by discussing the
2 current treatment options for the management of
3 acute postsurgical pain, followed by a brief
4 summary of the clinical development program for
5 this NDA. FDA's statistical reviewer, Katherine
6 Meaker, will review the efficacy data from the
7 applicant's clinical development program, and I
8 will discuss the clinical implications of these
9 results.

10 I will conclude our formal presentation with
11 an assessment of the safety data from the study
12 submitted in support of the NDA, including a
13 discussion of the previously identified safety
14 concerns and the applicant's response, followed by
15 a summary of the ongoing concerns. Of note, the
16 nomenclature for this investigational drug product
17 will be referred to as Posimir or SABER-bupivacaine
18 throughout my presentation.

19 I will now discuss current postsurgical
20 analgesic treatment options. Given the current
21 opioid crisis facing the United States,
22 postsurgical pain management via a multimodal,

1 perioperative approach has become a rapidly
2 advancing field. Currently approved non-opioid
3 analgesics include IV and oral NSAIDs and
4 acetaminophen. Additionally, unapproved anesthetic
5 adjuncts such as interoperative lidocaine and
6 ketamine infusions are also being used.

7 The administration of local anesthetics in
8 the perioperative period is a large part of the
9 multimodal approach to postoperative pain
10 management, including administered as wound
11 infiltration, peripheral nerve block, and neuraxial
12 block. Soft tissue procedures in general are most
13 amenable to local anesthetic wound infiltration and
14 orthopedic procedures most amenable to peripheral
15 nerve blockade.

16 There are currently no local anesthetic
17 products approved with extended-release labeling
18 language. While some local anesthetic products
19 such as SABER-bupivacaine may demonstrate a delayed
20 maximum plasma concentration, this has not
21 consistently resulted in demonstrated prolonged
22 duration of action when compared to

1 immediate-release products. Because local
2 anesthetics are locally-acting products, systemic
3 concentrations generally have no relationship to
4 the observed clinical effect. The most commonly
5 administered local anesthetics include lidocaine,
6 bupivacaine, ropivacaine, mepivacaine, and Exparel.

7 I will now discuss the clinical development
8 program for Posimir. The applicant's proposed
9 language for the indication is as follows.

10 "Posimir is an extended-release solution of
11 bupivacaine, an amide local anesthetic, indicated
12 for single-dose instillation into the surgical site
13 to produce postsurgical analgesia." The indication
14 during the initial NDA review cycle was for broad
15 postsurgical analgesia as well, but was worded
16 slightly differently.

17 NDA 204803 was received on April 12, 2013.
18 There were seven studies submitted in support of
19 the efficacy of SABER-bupivacaine, including two
20 studies described as pivotal by the applicant, one
21 in inguinal hernia repair and one in arthroscopic
22 surgery.

1 Upon completion of the clinical review, the
2 division determined that efficacy had been
3 established for arthroscopic shoulder surgery only
4 and communicated this to the applicant on January
5 14, 2014 in a discipline review letter and in a
6 teleconference held on January 17, 2014. The
7 identified safety concerns of possible
8 chondrolysis, wound-related adverse events, and
9 neurologically-related adverse events were also
10 conveyed during that time.

11 In response to the discipline review letter,
12 or DRL, the applicant submitted additional
13 information to support the efficacy of
14 SABER-bupivacaine in open inguinal hernia repair.
15 The medical officer at that time agreed that the
16 adequate evidence of efficacy had been established
17 for SABER-bupivacaine over SABER placebo, and also
18 that the risk of chondrolysis had been adequately
19 addressed such that the complete response letter
20 included three deficiencies related to the safety
21 findings in patients treated with SABER-bupivacaine
22 described in my next slide.

1 The division identified three deficiencies
2 related to safety findings in patients treated with
3 SABER-bupivacaine, and they were as follows:
4 adverse events related to the shoulder joint and
5 surrounding soft tissues; increased risk of
6 wound-related adverse events, that is bruising,
7 hematoma, pruritis, and dehiscence; an increase
8 incidence of neurologically-related adverse events,
9 including dizziness, dysgeusia, headache,
10 hypoesthesia, parasthesia, and somnolence.

11 The division conveyed to the applicant in
12 the complete response letter, or CR letter, that a
13 determination of whether SABER-bupivacaine
14 containing products resulted in clinically relevant
15 adverse events to a greater extent than non-SABER
16 containing products or bupivacaine treatments, and
17 that a determination cannot be made based on the
18 limited number of patients who received a non-SABER
19 containing treatment.

20 The division advised that the information
21 needed to resolve the deficiencies should include
22 an additional safety study as indicated in this

1 slide. The applicant was advised that all
2 additional safety studies need to include
3 SABER-bupivacaine and either bupivacaine
4 hydrochloride or a non-SABER containing placebo, or
5 both.

6 Subsequent to the issuance of the CR letter,
7 an end-of-review cycle meeting was held on
8 September 23, 2014 to discuss a possible path
9 forward for SABER-bupivacaine approval. The
10 discussion focused on additional information needed
11 to support a broad postsurgical analgesic
12 indication, including the need for an additional
13 study in a second soft tissue model.

14 Options for addressing the identified safety
15 concerns were also discussed. During this meeting,
16 the applicant indicated that for business reasons,
17 they no longer intended to seek an indication for
18 the treatment of postsurgical pain following
19 arthroscopic shoulder surgery.

20 The applicant submitted a formal dispute
21 resolution request on November 21, 2014 based on
22 disagreement with the division on how to adequately

1 address the safety issues identified in the CR
2 letter. In the formal dispute resolution request,
3 or FDRR, the applicant requested a determination of
4 both safety and efficacy despite the fact that the
5 CR letter contained only safety concerns. Based on
6 this request, the efficacy results were
7 re-evaluated, and the office deputy director at the
8 time, Dr. Thanh Hai, concluded that Posimir's
9 efficacy was modest, thereby requiring a more
10 careful consideration of the risks.

11 Regarding the options for addressing the
12 identified safety concerns, the following two paths
13 forward were proposed. The applicant could conduct
14 an additional clinical study to better characterize
15 a risk-benefit profile of SABER-bupivacaine, as was
16 described in the CR letter, or submit all the
17 information provided in the end of review of
18 background materials with justification as to why
19 it is supportive of a favorable risk-benefit
20 profile for SABER-bupivacaine. Because this
21 additional information was not included in the
22 original NDA submission, it could not be reviewed

1 for purposes of modifying the CR regulatory
2 decision. The formal dispute resolution was
3 denied.

4 Subsequent to the FDRR denial decision, the
5 applicant submitted a phase 3 protocol for
6 evaluation of SABER-bupivacaine in patients
7 undergoing a laparoscopic chondrolysis. The
8 initial study protocol included saline, a non-SABER
9 comparator, as recommended by the division to
10 further inform the safety concerns associated with
11 the administration of the SABER vehicle.

12 The division also recommended inclusion of
13 an active comparator, specifically bupivacaine, for
14 two main reasons. First, bupivacaine is the most
15 commonly used local anesthetic for postoperative
16 analgesia, and second because SABER-bupivacaine is
17 a new formulation, it would be difficult to make a
18 favorable risk-benefit assessment if there were
19 safety findings unique to SABER-bupivacaine and not
20 associated with bupivacaine.

21 The NDA resubmission was received on June
22 27, 2019 and included the post hoc safety analysis

1 conducted after issuance of the CR letter and
2 presented during the end-of-review cycle meeting,
3 and the results from the laparoscopic or lap chole
4 study.

5 Statistical reviewer Katherine Meaker will
6 discuss the efficacy results of the applicant's
7 supportive clinical studies in detail, but as a
8 brief overview, as you've already heard from the
9 applicant, studies were conducted in a variety of
10 soft tissue models and a single orthopedic model.
11 Specifically, there were three phase 2 studies
12 conducted in patients undergoing arthroscopic
13 shoulder surgery, two phase 2 studies conducted in
14 patients undergoing open inguinal hernia repair,
15 and several studies in other surgical models as
16 indicated.

17 The PERSIST study, an evaluation of
18 SABER-bupivacaine in patients undergoing lap chole,
19 was conducted primarily to address the safety
20 concerns identified in the CR letter, and in part
21 to provide additional efficacy information. I'll
22 now turn it over to Ms. Meaker.

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FDA Presentation - Katherine Meaker

MS. MEAKER: Thank you, Dr. Petit-Scott.

Earlier today, the applicant discussed two successful efficacy studies which demonstrated a statistically significant treatment effect versus SABER placebo, one, an arthroscopic shoulder surgery, and one, an inguinal hernia repair. The clinical development program for Posimir included eight studies, one an orthopedic model, and four soft tissue models, including abdominal and pelvic procedures.

This table shows the eight studies in Posimir in chronological order within surgical procedure. I will discuss the overall body of evidence from the eight studies and discuss statistical rationales for including efficacy evidence from each. The asterisk designates the two studies which the applicant considers as pivotal.

Note that two studies in abdominal laparoscopic procedures were designed as phase 3 studies, but the results did not demonstrate

1 superior efficacy, and the applicant has downplayed
2 their results. I will discuss the studies within
3 each surgical procedure separately.

4 Here are the three randomized-controlled
5 clinical studies in patients undergoing
6 arthroscopic shoulder surgery. CLIN005-0006 was
7 designed to evaluate two methods of administration
8 with two cohorts for randomization. The method
9 used in Cohort 2, subacromial administration, was
10 repeated in later shoulder surgery studies.
11 Results for Cohort 2 are reported here, as they are
12 applicable to the body of evidence for the current
13 intended dosing and administration. The sample
14 size of 24 patients per treatment arm was powered
15 to detect a difference in mean pain scores.

16 Study 803-017 was designed and powered to
17 test for superiority of Posimir versus SABER
18 placebo in this surgical setting but did not
19 achieve that goal. The results of Study BU-002-IM
20 demonstrated statistical significance for Posimir
21 versus SABER placebo, which was the primary
22 objective.

1 Here are the results from the three studies
2 in patients undergoing arthroscopic shoulder
3 surgery. For CLIN005-0006, Cohort 2 was
4 subacromial administration. The results did not
5 show statistical significance. Study 803-017 was
6 designed to test for superiority but did not
7 demonstrate statistical significance. The
8 estimated difference in mean pain used to power the
9 study was 1.9 units on the 11-point scale. The
10 observed difference was 0.6 units, less than a
11 third of what the applicant had anticipated when
12 planning the protocol. As previously noted,
13 Study BU-002-IM demonstrated statistical
14 significance for Posimir versus SABER placebo.

15 These forest plots present the efficacy
16 results from my previous slide. Posimir is labeled
17 SABER bupivacaine here. The control is SABER
18 placebo in all three studies. The treatment effect
19 in all three studies is in the direction to favor
20 Posimir over SABER placebo, but only one,
21 BU-002-IM, demonstrated a statistically significant
22 difference.

1 This plot displays the mean pain intensity
2 on movement at each measured time point after
3 surgery for the pivotal study, BU-002-IM. This is
4 the same information presented in applicant's
5 slide 46. The horizontal axis shows time after
6 surgery for day 0 through 3. The vertical axis
7 shows the 11-point pain on movement scale; lower
8 pain values are better.

9 The plot presents the mean pain scores for
10 each group at each time point. The primary
11 endpoint, mean pain for 0 to 72 hours, is a
12 weighted average of the pain scores shown here.
13 The bold solid line toward the bottom is the
14 Posimir group. The lighter solid line towards the
15 top is the SABER placebo group. The dotted line is
16 the bupivacaine 50-milligram group. The larger
17 separation between the lines in this plot is in the
18 0 to 24-hour time frame, day 0. This separation is
19 driving the results of the primary endpoint mean
20 pain on movement for 0 to to 72 hours.

21 To summarize the results in arthroscopic
22 shoulder surgery, all three studies were designed

1 and conducted as adequate and well-controlled
2 studies. The applicant now does not consider
3 Study CLIN005-0006, Cohort 2 as an adequate and
4 well-controlled study. This study had two cohorts,
5 each planned for a different approach for
6 administration of this study treatment into the
7 surgical site.

8 Based on powered calculations in the
9 protocol, the plan sample size of 24 per arm was
10 sufficient to test the comparison of groups in
11 Cohort 2. The results of Cohort 2 are informative
12 in the overall consideration of efficacy of Posimir
13 in this surgical procedure.

14 Next, I will discuss the two randomized-
15 controlled studies conducted in patients undergoing
16 inguinal hernia repair. CLIN005-0010 was designed
17 to compare two methods of administering study drug.
18 My analysis compares the two preplanned 5-milligram
19 dose randomized blinded treatment arms in Cohort 2.
20 I did not include any of the patients who received
21 7.5 milliliter after the amendment listed in the
22 applicant's slide 30, nor did I pool any placebo

1 treatment arms.

2 Although the sample size was powered to
3 detect a difference in pain scores, neither
4 administration method demonstrated statistical
5 significance for Posimir versus SABER placebo. As
6 shown in the first row, the direction of the
7 treatment effect favors placebo. CLIN803-006-0006
8 is considered pivotal by the applicant, although
9 designed as a phase 2 PK/PD dose-response study.

10 This forest plot shows the results from the
11 previous slide. Posimir is labeled as
12 SABER-bupivacaine. The control is SABER placebo in
13 both studies. The top line shows CLIN005-0010,
14 Cohort 2, with the direction of treatment effect in
15 favor of SABER placebo to the right of the vertical
16 line at zero. The lower line is
17 Study CLIN803-006-0006, which demonstrated a
18 statistically significant difference versus SABER
19 placebo.

20 This plot displays the mean pain at each
21 measured time point through 3 days after surgery
22 for the pivotal study in inguinal hernia. As in

1 the other pivotal study, the largest separation
2 between the lines is in the 0 to 24 hour time
3 frame, day 0, which is driving the results of the
4 primary endpoint, mean pain from 0 to 72 hours.

5 In the original submission, Study
6 CLIN005-0010 was identified by the applicant and
7 reviewed by FDA as a supportive study for efficacy
8 in inguinal hernia surgery. During the dispute
9 resolution process, FDA noted this study as
10 providing evidence of inconsistent efficacy. The
11 applicant has since reclassified this as
12 non-adequate and well controlled, thus lessening
13 the role of this study.

14 The next surgical model I'll discuss is
15 hysterectomy. The applicant conducted a single
16 randomized-controlled study in women undergoing
17 open hysterectomy surgery. The results of this
18 study did not demonstrate superiority of Posimir
19 versus SABER placebo, the primary objective. This
20 study also included an active control arm,
21 bupivacaine 100 milligrams shown on the second row.
22 This comparison was an exploratory analysis.

1 This plot shows the comparison of Posimir to
2 SABER placebo. The observed difference is small
3 and does not demonstrate statistical difference
4 between the groups. In summary, the results of
5 this single study do not support efficacy for this
6 surgical procedure.

7 Lastly, I will discuss studies conducted in
8 patients undergoing abdominal surgery. Although
9 planned as phase 3 studies, the applicant does not
10 designate them as pivotal. Study 803-025 included
11 three cohorts of patients, depending on type of
12 surgery. Cohort 1, patients underwent open
13 laparotomy; in Cohort 2, laparoscopic
14 cholecystectomy; in Cohort 3 laparoscopic assisted
15 colectomy. Only the sample size for Cohort 3 was
16 powered to detect a difference for Posimir versus
17 SABER placebo for mean pain on movement for 0 to 72
18 hours postsurgery.

19 I have separated PERSIST Part 1 and PERSIST
20 Part 2 here, as the designs were different with
21 different objectives. PERSIST Part 1 was planned
22 as a safety and efficacy study in patients

1 undergoing lap chole. The objective was to address
2 safety concerns in the complete response letter
3 from the initial submission, which was the reason
4 for the saline control group.

5 The applicant elected to stop enrollment in
6 Part 1 and drop the saline placebo group. This was
7 not the advice of the FDA. FDA did advise the
8 applicant of the need to assess efficacy versus an
9 active control in order to better understand the
10 benefit-risk relationship.

11 PERSIST Part 2 began with Amendment 3. The
12 double-blind comparator group was now active
13 control bupivacaine 75 milligrams. The protocol
14 was designed and powered to test superiority of
15 Posimir versus bupivacaine. All aspects of the
16 protocol submitted as amendment number 3 fulfilled
17 the requirements for an adequate and
18 well-controlled study. The later amendments listed
19 in applicant's slide 31 regarding additional safety
20 assessments did not impact the efficacy
21 assessments.

22 This table shows the results of

1 Study 803-025. This had three cohorts depending on
2 type of surgery. The control group in Cohorts 1
3 and 2 was bupivacaine 150 milligrams. Comparisons
4 of Posimir to control in these cohorts were planned
5 as exploratory. The results were later used to
6 design the PERSIST study.

7 Cohort 3 was powered to detect a difference
8 versus SABER placebo. The predicted difference for
9 planning was 1.1 units on the 0 to 11 pain scale.
10 The observed difference was 0.3, less than a third
11 of the anticipated treatment effect. There was
12 insufficient evidence to demonstrate Posimir was
13 superior to SABER placebo.

14 This table shows the results for each part
15 of the PERSIST study conducted in patients
16 undergoing lap chole procedure. PERSIST Part 1 was
17 designed and powered to compare Posimir to saline
18 placebo. PERSIST Part 2 was designed and powered
19 to test the superiority of Posimir versus active
20 control. However, the results did not show
21 sufficient evidence to conclude a statistically
22 significant difference between Posimir and

1 bupivacaine 75 milligrams.

2 The anticipated difference was 0.8 units
3 from mean pain on movement for 0 to 48 hours, the
4 primary endpoint in PERSIST Part 2. Mean pain for
5 0 to 72 hours was a secondary endpoint and is shown
6 here for consistency to all the other studies.

7 PERSIST Part 2 did not show a statistically
8 significant difference for mean pain on movement
9 for either of the plan time frames.

10 Here are the results for the three
11 comparisons in abdominal surgery procedures, which
12 were planned as phase 3 studies. 803-025, Cohort 3
13 patients underwent laparoscopic assisted colectomy.
14 The patients in both parts of the PERSIST study
15 underwent lap chole. Each had a different
16 comparator, but Posimir did not demonstrate
17 superiority in any of these studies.

18 In Study 803-025, Cohort 3, in patients
19 undergoing laparoscopic assisted colectomy, there
20 is a slight separation in the pain curves for
21 Posimir and SABER placebo. This is consistent with
22 the conclusion that there was insufficient evidence

1 to demonstrate superiority of Posimir versus SABER
2 placebo in this surgical model.

3 In the PERSIST Part 2 study, there was a
4 slight separation in the first 24 hours after
5 surgery, but no clear separation of the pain curves
6 for Posimir and bupivacaine 75 milligrams beyond
7 that time frame. This is consistent with the small
8 difference observed in the mean pain on movement
9 for the 0-to-72 hour endpoint and the conclusion
10 that this study did not provide sufficient evidence
11 to demonstrate superiority of Posimir versus
12 bupivacaine 75 milligrams.

13 In summary, for abdominal surgical
14 procedures, neither of the phase 3 studies achieved
15 the desired objective. In my review of the PERSIST
16 study, I consider Part 1 and Part 2 as adequate and
17 well-controlled clinical studies, each designed
18 with a different objective. PERSIST Part 1
19 included a saline control arm, rather than SABER
20 placebo, to address concerns in the complete
21 response letter after the initial submission.
22 PERSIST Part 2 included an active control

1 bupivacaine arm to address later advice from FDA.

2 The role of this study is not agreed upon.

3 Here's our summary of the eight randomized
4 double-blind controlled clinical studies which
5 provide information to the overall body of evidence
6 to be considered for this application. The phase 2
7 studies were designed appropriately to direct the
8 clinical development with respect to dosing and
9 administration. The objective of the phase 3
10 studies in abdominal surgical procedures was to
11 show superiority of Posimir to SABER placebo or
12 active control.

13 While the direction of the treatment effect
14 favors Posimir on most studies, only the two
15 studies the applicant highlights demonstrate
16 statistically significant evidence of efficacy.
17 The applicant has minimized the role of three
18 studies, marked in the right-hand column. The
19 first two were included as supportive evidence in
20 the original submission and were later reclassified
21 as non-adequate and well-controlled by the
22 applicant in the resubmission. One, inguinal

1 hernia repair showed a treatment effect in the
2 direction favoring placebo over Posimir, though not
3 statistically significant.

4 The applicant discredits PERSIST Part 2
5 despite this being specifically designed to compare
6 Posimir to bupivacaine 75 milligrams active
7 control. The rationale given by the applicant do
8 not warrant ignoring these results when considering
9 the full body of evidence to characterize efficacy.

10 This displays all the preplanned
11 comparisons, which provide information to the
12 decision regarding efficacy of Posimir in a variety
13 of surgical procedures. This plot does not include
14 exploratory comparisons to bupivacaine active
15 control arms. The two studies, which the applicant
16 designated as pivotal, are the only two which
17 demonstrate statistical significance indicated by
18 the entire confidence interval being to the left of
19 the vertical line at zero.

20 After dispute resolution of the original
21 submission, FDA concluded evidence of efficacy was
22 modest and inconsistent. Although the PERSIST

1 study was designed to address FDA concerns, the
2 results do not change that conclusion. The results
3 from the randomized-controlled clinical studies are
4 inconsistent within surgical procedures the
5 applicant planned to demonstrate efficacy and do
6 not consistently show superiority of Posimir versus
7 SABER placebo. When a treatment effect is detected
8 for pain on movement of 0 to 72 hours after
9 surgery, the majority of the treatment effect is
10 observed in the first 24 hours after treatment, as
11 shown by separation of the lines on the plots of
12 pain over 3 days after surgery.

13 Now, Dr. Petit-Scott will discuss the
14 clinical relevance of efficacy and the safety
15 results from the clinical development program.

16 **FDA Presentation - Renee Petit-Scott**

17 DR. PETIT-SCOTT: This table summarizes the
18 shoulder studies conducted by the applicant,
19 organized beginning with the oldest to the most
20 recent study. As discussed by Ms. Meaker, the most
21 recently completed study, Study BU-002-IM, was the
22 only study that demonstrated a statistically

1 significant difference in pain intensity with
2 movement and opioid rescue analgesia through
3 72 hours in patients treated with SABER-bupivacaine
4 compared to those treated with SABER placebo.

5 This study arguably evaluated the least
6 invasive procedures. Specifically, Study BU-002-IM
7 evaluated patients undergoing arthroscopic shoulder
8 procedures only, including subacromial
9 decompression. No patient underwent an open
10 procedure in this study. This is in contrast to
11 the other two shoulder studies in which patients
12 underwent more extensive and open procedures. For
13 example, in Study CLIN005-0006, evaluated
14 procedures included rotator cuff repair, glenoid
15 labrum repair, and biceps tenodesis. In
16 Study C803-017, evaluated procedures included an
17 open distal clavicle excision or a Mumford
18 procedure.

19 As discussed by Ms. Meaker, all studies used
20 the SABER comparator in the primary analysis. The
21 analysis in study BU-002-IM comparing low dose,
22 that is 50 milligrams of bupivacaine to

1 SABER-bupivacaine, did not demonstrate a
2 statistically significant difference in mean pain
3 intensity with movement. The sum total of these
4 results from the shoulder study suggests that
5 SABER-bupivacaine appears to improve postoperative
6 pain with movement above SABER placebo only in
7 limited arthroscopic shoulder procedures in
8 patients with an intact rotator cuff.

9 Open inguinal hernia repair is a widely used
10 surgical model to demonstrate the safety and
11 efficacy of local anesthetic products due to the
12 relative benign nature of the procedure and the low
13 postoperative complication rate. In this slide,
14 the studies are ordered by completion date with the
15 oldest study listed first. Study CLIN803-006-0006
16 is considered the pivotal study by the applicant.

17 The study design issues described by the
18 applicant likely contributed to lack of
19 demonstrated efficacy in Study CLIN005-0010,
20 however as described by the statistical reviewer
21 during review of the original NDA, the
22 SABER-bupivacaine treated patients reported more

1 pain and required more opioid rescue medication
2 than SABER placebo-treated patients.

3 Furthermore, based on concern that the
4 primary endpoint of mean pain intensity through 120
5 hours in this study was too long an additional
6 analysis of mean pain intensity with movement
7 through 72 hours was conducted. This was the
8 primary endpoint in the successful inguinal hernia
9 study, Study CLIN803-006-0006. This exploratory
10 analysis also did not demonstrate a statistically
11 significant difference in patients treated with
12 SABER-bupivacaine compared to those treated with
13 SABER placebo, and in fact the results favored
14 SABER placebo.

15 Unlike the orthopedic evaluations, the
16 applicant conducted efficacy evaluations in a
17 variety of soft tissue surgical procedures,
18 including pelvic and abdominal procedures and those
19 performed both open and laparoscopically. The only
20 two phase 3 studies conducted by the applicant were
21 in soft tissue models and included patients
22 undergoing laparotomy, lap chole, or lap-assisted

1 colectomy in Study C803-025 and patients undergoing
2 lap chole in Study C803-028.

3 Neither study demonstrated a statistically
4 significant difference in pain intensity with
5 movement in patients treated with SABER-bupivacaine
6 compared to the respective control, which was SABER
7 placebo in Study C803-025 and bupivacaine in
8 Study C803-028.

9 As discussed by Ms. Meaker, Part 2 of the
10 PERSIST study is considered adequate and well
11 controlled by FDA, despite the lack of demonstrated
12 efficacy. It is worth noting that the primary
13 efficacy endpoint selected for this part of the
14 study was mean pain intensity with movement through
15 only 48 hours versus 72.

16 This change in duration of AUC was not a
17 recommendation of the FDA. The results from Part 2
18 of this study suggests that SABER-bupivacaine is
19 likely no more efficacious than immediate-release
20 bupivacaine for the management of acute
21 postsurgical pain following lap chole.

22 While the regulatory threshold for approval

1 does not require the demonstration of superiority
2 over an active comparator, the previously
3 identified and ongoing safety issues make the lack
4 of a demonstrated clinical benefit over standard of
5 care immediate-release bupivacaine more clinically
6 relevant.

7 In conclusion, the efficacy findings are as
8 follows. Efficacy was demonstrated in 1 of 5 soft
9 tissue surgeries and 1 of 3 orthopedic studies
10 conducted by the applicant; in other words, only a
11 single study, each in one soft tissue and one
12 orthopedic model, and won on the primary efficacy
13 endpoint. Studies conducted in the same or similar
14 surgical models did not demonstrate statistically
15 or clinically significant differences in patients
16 treated with SABER-bupivacaine compared to those
17 treated with SABER placebo.

18 The studies that the applicant has elected
19 to remove from the overall assessment of efficacy
20 were adequate and well controlled such that the
21 statistical analysis plan was appropriate for
22 detecting the stated difference in the endpoint

1 analyses.

2 Evaluation of the pain curves for
3 SABER-bupivacaine and SABER placebo treatment
4 suggests that early analgesia, that is within the
5 first 24 hours in the postoperative period, is
6 likely driving the statistical significance. The
7 difference at later time points are less
8 impressive.

9 The demonstration of efficacy beyond the
10 placebo treatment is not clinically meaningful and
11 may mislead clinicians and patients in shaping
12 postoperative expectations. Additionally, a
13 statistically significant improvement above a
14 placebo treatment of 1.1 to 1.3 points on an
15 11-point pain scale is not clinically meaningful.

16 Lastly, based on the PK data for
17 SABER-bupivacaine, additional local anesthetic
18 administration through 96 hours is contraindicated,
19 suggesting that for patients in whom
20 SABER-bupivacaine is not efficacious, alternate
21 pain management is limited to oral and IV
22 analgesics, including opioids. Given the overall

1 lack of a consistently demonstrated benefit of
2 SABER-bupivacaine administration, it seems there
3 will be a very high percentage of postoperative
4 patients who would be impacted by this limitation.

5 I will now shift gears and discuss the
6 safety concerns previously identified, as well as
7 those remaining. As previously mentioned, the
8 division identified three deficiencies related to
9 safety findings in patients treated with
10 SABER-bupivacaine in the initial NDA review.

11 As a brief review recap, they were adverse
12 events related to the shoulder joint and
13 surrounding tissue; increased wound-related
14 adverse events, including bruising, hematoma,
15 pruritis, and dehiscence; and an increased risk of
16 neurologically-related adverse events, including
17 dizziness, dysgeusia, headache, hypoesthesia,
18 parasthesia, and somnolence.

19 In an attempt to address the safety concerns
20 identified in the CR letter, the applicant has
21 submitted additional safety information from
22 previously completed studies and conducted the

1 additional PERSIST study, as has already been
2 described. The results of the additional analyses
3 from the shoulder studies will be discussed first,
4 followed by a discussion of the wound-related and
5 neurologically-related adverse events from the
6 PERSIST study, and previously completed studies as
7 necessary.

8 This slide summarizes the follow-up
9 evaluations for each study conducted in patients
10 undergoing shoulder surgery listed in chronological
11 order. The evaluation conducted by the applicant
12 in patients in Study CLIN005-0006 included review
13 of the 14-day follow-up data, as well as a 10-year
14 written follow-up investigator survey.

15 The additional evaluations conducted by the
16 applicant in patients who underwent a shoulder
17 procedure in Study C803-017 included the following.
18 Two blinded orthopedic surgeons re-read baseline
19 and follow-up MRIs for the three patients suspected
20 of having post-arthroscopic glenohumeral
21 chondrolysis, or more simply, chondrolysis.

22 A blinded radiologist re-read baseline and

1 follow-up MRIs in all study patients, and any
2 relevant changes were further evaluated by an
3 orthopedic surgeon. Review of 18-month, follow-up
4 physical examinations were completed by blinded
5 investigators.

6 The additional safety information and
7 analyses from Study C803-017 are the most
8 supportive of the safety profile of
9 SABER-bupivacaine when administering during
10 arthroscopic shoulder surgery. This shoulder study
11 had the longest duration of postoperative
12 follow-up, that is 18 months, and the re-reading of
13 MRIs conducted during that visit did not identify
14 any additional concerning findings.

15 Furthermore, while there does not appear to
16 have been routine follow-up beyond 18 months, it
17 seems unlikely that there would be adverse events
18 yet to be reported and that the applicant would be
19 unaware of. The evaluation conducted by the
20 applicant in patients in Study BU-002-IM included
21 review of the 6-month follow-up data. Specific
22 follow-up findings from each study are presented in

1 the next slide.

2 It does not appear that there were any real
3 cases of chondrolysis and no follow-up MRI
4 identified loss of articular cartilage.
5 Additionally, the follow-up physical examination
6 data from patients in Studies CLIN005-0006 and
7 C803-017 did not identify consistent clinically
8 significant decreases in function or persistent
9 pain in patients treated with SABER-bupivacaine
10 compared to those treated with SABER placebo. It
11 is worth noting, however, that these studies did
12 not use a non-SABER containing comparator such that
13 the true incidence of adverse events related
14 specifically to the SABER vehicle in these studies
15 is difficult to determine.

16 Study BU-002-IM was the only shoulder study
17 which evaluated a non-SABER containing comparator,
18 bupivacaine. The safety results from this study
19 are the least supportive of the safety of
20 SABER-bupivacaine for three reasons.

21 First, there were changes noted on the
22 6-month follow-up MRI in patients treated with a

1 SABER containing product that were different than
2 those observed in patients treated with
3 bupivacaine. Those changes included moderate bone
4 erosion and edema, mild to moderate
5 musculo-tendinous abnormalities, mild shoulder
6 joint changes, and mild tissue abnormality or
7 scarring.

8 Overall, there were fewer patients who had
9 improved postoperative MRI imaging in SABER
10 treatment groups compared to the bupivacaine
11 treatment group. Of note, there was a single
12 patient treated with bupivacaine who had severe
13 fluid collection and bone edema and a single
14 patient treated with SABER placebo who had a severe
15 effusion in the subcoracoid bursa noted on
16 postoperative MRI.

17 Second, mean postoperative Constant-Murley
18 scores increased in all treatment groups, but the
19 least in the SABER-bupivacaine treated patients.
20 Constant-Murley assessment includes both
21 subjective, pain and activities of daily living,
22 and objective, strength and range of motion

1 variables, to comprehensively evaluate shoulder
2 joint function.

3 Third, there were 7 patients with worsening
4 CM scores postoperatively. Five were treated with
5 SABER-bupivacaine and two were treated with SABER
6 placebo. The MRIs in these patients were
7 reportedly unchanged from baseline.

8 The results of the follow-up evaluations
9 from patients treated in Study BU-002-IM are not as
10 supportive of the safety profile with
11 SABER-bupivacaine when administered during
12 arthroscopic shoulder surgery. While there does
13 not appear to have been routine follow-up beyond
14 6 months, this study was completed nearly 10 years
15 ago, and it seems unlikely that there would be
16 adverse events yet to be reported and that the
17 applicant would be unaware of.

18 In an attempt to address the wound-related
19 safety concerns identified in the CR letter,
20 including bruising, hematoma, pruritis, and
21 dehiscence, the applicant conducted the PERSIST
22 study, employing safety monitoring recommended by

1 the FDA. The division advised the applicant to
2 thoroughly evaluate six prespecified wound-related
3 adverse events, which included peri-incisional
4 bruising, wound hematoma, wound dehiscence,
5 surgical site infection, surgical site bleeding,
6 and drainage from the surgical incision. The
7 incidence of these adverse events reported by the
8 applicant is shown in the next slide.

9 This table taken from the applicant study
10 report indicates that there was an increased
11 incidence of bruising in both parts of the study,
12 an increased incidence of surgical site bleeding in
13 Part 1 and an increased incidence of drainage,
14 hematoma, and surgical site infection in Part 2.
15 Drainage from the surgical site was generally
16 serosanguinous with the exception of a single case
17 of purulent discharge in a patient treated with
18 bupivacaine and will not be discussed further.

19 There were 5 cases of wound dehiscence in
20 Part 2 of the study. These events were described
21 as superficial separation of the wound edges, most
22 commonly at the umbilical or epigastric incisions,

1 and all resolved without treatment.

2 These findings are in contrast to the
3 observations made during review of the original NDA
4 submission, suggesting the length of the surgical
5 incision may play a role in the development of
6 wound dehiscence. Each of the remaining
7 wound-related adverse events will be discussed in
8 more detail in the following slides.

9 This figure taken from the applicant's study
10 report summarizes the mean total bruise area in
11 square centimeters on the Y-axis by study day on
12 the X-axis. Not only was there an increased
13 incidence of bruising in patients treated with
14 SABER-bupivacaine in both parts of the study that
15 was noted during the applicant's presentation, but
16 the overall size of the bruising was also increased
17 as indicated in this figure.

18 Additional evaluation indicates that all
19 patients with any bruising 100 square centimeters
20 or greater were treated with SABER-bupivacaine in
21 either Part 1 or Part 2 of the study; 100 square
22 centimeters is equal to 15.5 square inches, which

1 represents a circular area of approximately 4 and a
2 half inches in diameter. For reference, an average
3 man's palm is approximately 3 and a half inches in
4 diameter.

5 The largest bruise reported for the
6 SABER-bupivacaine treatment was 440 square
7 centimeters; for the bupivacaine treatment group,
8 it was 66 square centimeters; and for the saline
9 placebo treatment group, it was 40 square
10 centimeters. While bruising may not represent a
11 concerning adverse event in isolation, it may
12 potentially mask or predispose to more concerning
13 adverse events such as infection or hematoma.

14 Surgical site bleeding was rated as spotting
15 of the dressing, soaking of the dressing, or
16 continuous bleeding throughout the study. The
17 majority, that is greater than 90 percent, of
18 bleeding from the umbilical incision on the day of
19 surgery involved only spotting of the dressing.

20 However, in Part 1 of the study, there was a
21 higher incidence of a soaked dressing in the
22 SABER-bupivacaine group compared to the saline

1 group, that is 6 percent versus 0 percent,
2 respectively. In Part 2 of the study, the
3 incidence of soaked dressing bleeding was similar
4 between treatment groups on the day of surgery.

5 A potential issue in the table displayed is
6 the duration of surgical site bleeding after
7 treatment with SABER-bupivacaine compared to
8 treatment with either control in each part of the
9 study. Specifically, it appears that there was a
10 higher incidence of bleeding through day 8 or
11 postoperative day 7 in patients treated with
12 SABER-bupivacaine. Additionally, there was a
13 patient treated with SABER-bupivacaine in Part 1 of
14 the study who had a soaked dressing at the
15 epigastric incision on study day 4.

16 While the overall number of patients with
17 bleeding on study days 4 through 8 are low, the
18 results are more relevant in the setting of the
19 previously identified and ongoing safety concerns
20 associated with administration of
21 SABER-bupivacaine. The reported incisional
22 bleeding on day 8 was spotting of the dressing only

1 for all treatment groups.

2 In Part 2 of the study, the incidence of
3 postoperative wound hematoma was higher in the
4 SABER-bupivacaine treatment group compared to the
5 bupivacaine treatment group. Specifically, the
6 incidence of wound hematoma was 4 percent versus 1
7 percent, respectively. Almost all hematomas
8 occurred on study days 4 or 8 at the umbilical
9 incision. Two patients in the SABER-bupivacaine
10 group and one patient in the bupivacaine group had
11 more than one hematoma. The applicant stated that
12 all but one hematoma was reported by two
13 investigative sites, suggesting that potentially
14 those sites overcalled any swelling of the wound a
15 hematoma.

16 There were 7 patients with surgical site
17 infection, five treated with SABER-bupivacaine and
18 two treated with bupivacaine. The umbilical
19 incision was involved in most cases. They were
20 considered superficial and resolved within 28 days
21 of oral antibiotic administration. The applicant
22 has stated that the overall incidence of surgical

1 site infection is consistent with reports in the
2 published literature ranging from 0.8 to
3 4.1 percent, and that all cases resolved with oral
4 antibiotics, and no additional complications were
5 observed.

6 While the incidence may not be unexpectedly
7 high and consistent with reports in the literature
8 and all did resolve with oral antibiotic
9 administration, this increased incidence, in
10 combination with other wound-related adverse events
11 in patients treated with SABER-bupivacaine,
12 negatively impacts the benefit-risk profile of this
13 drug product. Furthermore, the likely broad
14 postmarket exposure and the potential impact on
15 many surgical patients undergoing a variety of
16 surgical procedures is concerning.

17 Consistent with the local inflammatory
18 reaction, there was a consistently larger portion
19 of patients treated with SABER-bupivacaine in both
20 parts of the study who experienced increases in
21 both leukocyte and neutrophil counts on study
22 day 4. The differences either resolved or were

1 less impressive on study day 29.

2 Additionally, there was a larger proportion
3 of patients treated with SABER-bupivacaine in both
4 parts of the study who experienced a shift from
5 normal to high creatine kinase levels, suggesting
6 an inflammatory reaction involving muscle tissue.
7 There were 7 patients with elevations of greater
8 than 2 times the upper limit of normal, 6 of whom
9 were treated with SABER-bupivacaine.

10 One patient treated in Part 1, who received
11 SABER-bupivacaine, had an elevation of greater than
12 7 times the upper limit of normal on study day 4,
13 which returned to normal by study day 9, an
14 unscheduled visit. This patient also had a mild
15 elevation in AST noted on study day 4, which also
16 resolved by study day 29.

17 Reported adverse events for this patient
18 included headache, peri-incisional bruising,
19 drowsiness, and nausea. Surface area of this
20 patient's largest bruise was 294 square
21 centimeters. Observed elevations in CK resolved
22 and there were no clinically relevant differences

1 between treatment groups by study day 29.

2 Moving on to the incidence of
3 neurologically-related adverse events, the division
4 requested the applicant evaluate 10 symptoms of
5 interest related to possible benzyl alcohol
6 toxicity, a component in the SABER vehicle as
7 you've already heard this morning. Because the
8 half-life of benzyl alcohol is short, this table,
9 provided by the applicant in response to an
10 information request, represents those symptoms
11 observed within 6 hours postoperatively.

12 The data indicates there was an increased
13 incidence in somnolence, headache, pruritis, and
14 dysgeusia in patients treated with
15 SABER-bupivacaine compared to those treated with
16 saline placebo or bupivacaine. Because somnolence,
17 headache, dysgeusia, and pruritis were observed
18 with greater frequency in SABER-treated patients in
19 the clinical studies evaluated during the original
20 NDA review, there was concern that exposure to
21 systemic benzyl alcohol may in fact be the cause.

22 Moving on to a brief discussion of the

1 additional safety information submitted from the
2 post-CR action analyses of the data submitted in
3 the initial NDA submission. The applicant has
4 evaluated wound-related adverse events from the
5 studies conducted in patients undergoing inguinal
6 hernia repair, hysterectomy, laparotomy, lap chole,
7 lap-assisted colectomy, and shoulder procedures,
8 and has determined that bruising was the only
9 adverse event consistently reported with an
10 increased incidence in patients treated with a
11 SABER product.

12 The additional information submitted
13 suggests that the difference in incidence of wound
14 dehiscence between SABER and non-SABER treatment
15 groups may have been influenced by data collection
16 procedures and patient-dependent assessments,
17 however, for longer incisions, there still may be
18 an increased risk. There did not appear to be any
19 reported cases of abnormal wound healing or
20 long-term wound complications in patients treated
21 with SABER-bupivacaine.

22 In general, review of this information from

1 post hoc safety analyses is more supportive of the
2 safety of SABER-bupivacaine administration in the
3 surgical models evaluated. Similarly, review of
4 the additional information provided for nervous
5 system related adverse events is more supportive of
6 the safety profile of SABER-bupivacaine.

7 The applicant has provided a rationale for
8 the identified imbalance in nervous system related
9 adverse events in patients treated with a SABER
10 containing product, suggesting that it was due to
11 the varied methods for adverse event collection;
12 specifically whether the adverse events were
13 spontaneously reported or queried. In the SABER
14 placebo-controlled studies, potential benzyl
15 alcohol related adverse events were solicited and
16 recorded using daily diaries.

17 In the bupivacaine-controlled studies, the
18 same adverse events were reported spontaneously and
19 not queried such that there may have been a falsely
20 observed increase in SABER placebo-controlled
21 studies. The applicant has stated that when the
22 adverse events were analyzed from studies using the

1 same collection methods, headache was the only
2 adverse event reported with an increased frequency,
3 and that data was presented this morning from the
4 applicant. Similar to the additional safety
5 information presented for wound-related adverse
6 events, this additional information post hoc
7 analyses is more supportive of the safety profile
8 of SABER-bupivacaine.

9 In conclusion, the post hoc analyses
10 provided by the applicant in response to the CR
11 letter appear to offer more support for the safe
12 administration of SABER-bupivacaine in the surgical
13 populations evaluated during clinical development.
14 Regarding the safety data from the PERSIST study,
15 there appear to be wound-related and
16 neurologically-related adverse events related to
17 the administration of SABER-bupivacaine in patients
18 undergoing lap chole. As previously discussed, the
19 increase incidence of neurologically-related
20 adverse events may be related to the systemic
21 exposure to benzyl alcohol.

22 In conclusion, while the ongoing safety

1 issues may be subtle and of low number, and
2 consistent with the incidences reported in the
3 published literature, as stated by Dr. Thanh Hai
4 during review of the formal dispute resolution
5 request, the safety findings require a more careful
6 consideration based on the demonstration of modest
7 efficacy in two of many evaluated surgical
8 procedures. Thank you.

9 **Clarifying Questions**

10 DR. LITMAN: Now we're going to proceed
11 to -- I think we're a little bit early, which is
12 great, because I think we're going to need the
13 time.

14 Are there any clarifying questions for the
15 FDA or for any of the speakers? Please remember to
16 state your name for the record before you speak.
17 If you can, please direct questions to a specific
18 presenter. And as I've emphasized, or tried to
19 emphasize before, please be as precise as possible
20 with clarification of the data that was presented.

21 (No response.)

22 DR. LITMAN: There are no clarifying

1 questions for the FDA?

2 (No response.)

3 DR. LITMAN: Okay. Then I'll start. My
4 general feeling here coming today is that I was not
5 prepared for a lot of the data that the sponsor
6 showed vis-a-vis the FDA briefing packet. So it's
7 kind of confusing to me, and I would like to hear
8 from other panelists whether or not they felt the
9 same, or I really do want to encourage people to be
10 devil's advocates and speak out on the opposite
11 view, too, as to whether or not they felt
12 comfortable with what was in the FDA briefing
13 packet, which was not what the sponsor showed
14 earlier this morning.

15 On one hand, it feels like this committee is
16 caught between two different points of view,
17 between the sponsor, and they're asking us to
18 consider their post hoc cumulative data, and the
19 FDA, which is looking at mainly the PERSIST study
20 as their pivotal evidence with which to make a
21 decision whether or not this drug is approved, and
22 it's confusing to me.

1 So with that in mind, are there any other
2 questions to the FDA? Dr. Z?

3 DR. ZACHAROFF: Hi. Kevin Zacharoff here.
4 I guess this question would be for Ms. Meaker.
5 With respect to the presentation and the
6 observations about benefits with respect to pain
7 score, I'm making the assumption that there was
8 control in the data analysis for use of rescue
9 medication, so that was factored out as a possible
10 issue.

11 If we were to look at need for a rescue
12 medication, we would probably see that it was
13 equivalent across all situations, and then we
14 consider the change in pain score to be the same?
15 Is that a rational conclusion?

16 MS. MEAKER: This is Kate Meaker,
17 statistical reviewer. The analyses for the pain
18 endpoints in this study and typical pain analyses
19 do account for use of rescue, and that's by
20 measuring the pain when rescue is requested prior
21 to it being administered. Does that answer your
22 question or was there a part 2?

1 DR. ZACHAROFF: Well, I guess what I'm
2 really asking is if we were to look a little bit
3 closer, is it possible we might have seen in the
4 placebo group that there was more rescue medication
5 that was given that could have sort of minimized
6 the difference in pain scores? Or if we were to
7 look at all the data, would we see that the rescue
8 medication request was similar between the groups
9 who had placebo, similar between the groups that
10 had study drug and normal bupivacaine, et cetera?

11 MS. MEAKER: Request for rescue was higher
12 in placebo, and that was adjusted by taking the
13 pain score, presumably a high pain score, prior to
14 receiving rescue, and that is carried forward for
15 an appropriate amount of time for the type of
16 rescue. So the analysis imputes that bad, high
17 pre-rescue score, pain score, for placebo patients
18 as it does for any patient requesting rescue. The
19 presumably high pain score prior to rescue is
20 carried forward, and the length of time depends on
21 the type and dosing of rescue.

22 DR. ZACHAROFF: One more question. Ms.

1 Meaker, this is probably not for you. This is more
2 along the clinical lines, so this would be for
3 Dr. Petit-Scott.

4 At any point in time, over the course of
5 time that this drug was evaluated and the
6 communications from the FDA to the sponsor, was
7 there ever a request made to see how this
8 medication would behave in the environment of a
9 local anesthetic being delivered to the patient for
10 the surgical procedure, as opposed to a general
11 anesthetic, so we could make some determination
12 about what kind of guidance to give
13 anesthesiologists or surgeons when a local
14 anesthetic load is already delivered to the patient
15 and this medication is being considered for
16 postoperative pain management?

17 DR. PETIT-SCOTT: Renee Petit-Scott. I
18 don't know. I wasn't involved with our early
19 review of the data submitted in the initial NDA
20 review, but my understanding is that from the
21 beginning, the plan was for all of the patients to
22 always be under general anesthesia. There was no

1 modification for a nerve block or neuraxial
2 anesthesia. It was all general anesthetic cases.

3 DR. ZACHAROFF: So that would lead me to
4 conclude, then, that we don't have any data to tell
5 us about how this medication should be used if the
6 anesthetic provided for the surgical procedure
7 involved a local anesthetic.

8 DR. PETIT-SCOTT: That's correct. Part of
9 the, I guess, decision to include only patients
10 under general anesthesia is based on the overall
11 dose of bupivacaine, 660 milligrams. So there may
12 have been discussion -- and again, I wasn't privy
13 to them early on, but it's a pretty big dose of
14 bupivacaine, so potentially put the patients under
15 general anesthesia to eliminate all other local
16 anesthetic administration.

17 DR. ZACHAROFF: Okay. Well, we can
18 editorialize on that later this afternoon. Thank
19 you.

20 DR. LITMAN: Thanks. Dr. Horrow?

21 DR. HORROW: Jay Horrow. I have a question
22 for Ms. Meaker relating to slide 19 of the FDA

1 presentation for clarity. I have general concerns
2 about the way data have been presented by both the
3 sponsor and the agency, which I would like to
4 discuss when we have our general discussion later
5 on. But the impression given with this slide is
6 that there's front loading of the outcome variable
7 in the first day.

8 The question I have is whether the agency
9 conducted any analyses of the separate individual
10 points in days 1, 2, and 3 to justify the claim
11 that there was frontloading of the outcome
12 variable? Thank you.

13 MS. MEAKER: Kate Meaker, statistical
14 reviewer. I assume by the phrase frontloading that
15 you mean that the weight given to the time points
16 in the first 24 hours play a more prominent role in
17 the calculation because there's more of them.

18 DR. HORROW: This is Jay Horrow. The
19 outcome variable is the sum of pain intensity
20 differences out to 72 hours. The visual impression
21 here is that most of the difference is in the first
22 day and that there's not much different later. Did

1 you look at differences in the later time points?

2 MS. MEAKER: Kate Meaker again. The primary
3 endpoint, 0 to 72 hours, is what's called an AUC.
4 It's a weighted average across time. So any time
5 point shown on the horizontal axis here is given
6 equal weight in the final calculation. We did look
7 at results at different time points. During the
8 first -- the sponsor's slide 46 showed this same
9 data but with error bars. There are statistically
10 significant differences through the first 12 hours,
11 but not beyond that point.

12 DR. HORROW: Jay Horrow. Thank you. I'm
13 just going to follow up on the clarity here. By
14 saying area under the curve, does that mean that
15 drawing straight lines between the individually
16 assessed data points, that we're including the area
17 under those presumably linear relationships in
18 between access to data points?

19 MS. MEAKER: Yes, mathematically speaking,
20 that is what area under the curve is doing. We
21 request pain scores more frequently during the
22 first 24 hours, but we adjust for the amount of

1 time. The weight in the weighted average is based
2 on those increments of time.

3 DR. HORROW: Thank you.

4 DR. LITMAN: Dr. Shoben?

5 DR. SHOBNEN: This is Abby Shoben. I'm not
6 actually sure who this question would go for. It's
7 a question about the outcome, but I think it's more
8 clinically based, which is to say there's some
9 suggestion in the FDA remarks that the difference
10 that was observed is not particularly clinically
11 meaningful. I was wondering what sort of
12 difference on an 11-point pain scale would be
13 clinically meaningful, both from the perspective of
14 what was approved for bupivacaine and what these
15 trials were powered for.

16 DR. ROCA: This is Rigo Roca. As you heard
17 from the presentation before, the trials were
18 powered for a particular difference. You may have
19 heard us say it was a 1.9 difference. As to
20 whether that was clinically meaningful at the time
21 of discussion of the trial, I'm not sure that we
22 actually stipulated.

1 You have to have a difference of 3 points,
2 or 5 points, or whatever, and a lot of times what
3 you end up doing is the applicant, the sponsor,
4 identifies a threshold that they're looking for.
5 They need to provide rationale as to why they feel
6 that may be clinically meaningful. As you can
7 suspect, at the end of the day, all the data comes
8 in and you evaluate it with respect to whether that
9 treatment effect that you're seeing actually is
10 clinically meaningful, depending on all the other
11 information, including safety.

12 DR. LITMAN: I have a couple of questions as
13 long as I don't see anybody else's -- Mr. O'Brien,
14 please?

15 MR. O'BRIEN: Thank you. Well, my questions
16 actually were for the sponsor, but I guess I'll
17 revert it to the FDA as well. Perhaps, Dr. Renee
18 Scott, if I could ask you, just for the clinical
19 significance. I was curious. If I heard you
20 correctly, what I heard you say was when the
21 sponsor came back and separated out the data by
22 solicited and unsolicited because of confounding,

1 you accepted that data as being more powerful
2 evidence for adverse events. Did I hear that
3 correctly?

4 DR. ROCA: This is Rigo Roca again. No,
5 that is not correct. In the context of when the
6 sponsor was looking at a safety data, trying to
7 figure out what it was, one of the things that was
8 entertained was, gee, does it make a difference
9 whether it's solicited or unsolicited? Usually
10 when a company or a sponsor comes in and suggests
11 additional ways to look at it, our response is, as
12 you would expect -- it's post hoc -- is to say,
13 sure, go ahead, do it. We don't tell applicant not
14 to do a particular analysis. We acknowledge there
15 will be caveats with respect to that particular
16 analysis because it is post hoc.

17 So it's not a matter that we told them, yes,
18 they could do it, encouraged them, or directed them
19 to do it. It's one of those things that an
20 applicant comes in, makes a suggestion of an
21 analysis, and most of the time we allow them to do
22 it with caveats.

1 MR. O'BRIEN: My question specifically had
2 to do with clinically significant issues for
3 patients, particularly nausea and vomiting. When I
4 look at those adverse events -- because it seemed
5 to me, when I compared it against the placebo data,
6 that in fact we had a higher incidence of vomiting
7 for the SABER [indiscernible], Posimir, than we did
8 with placebo, which was very interesting to me,
9 particularly with regard to the fact that with a
10 placebo population, they were getting more rescue
11 medication.

12 So it seemed to be counterintuitive that
13 those who were getting more opioids would in fact
14 have less or equal amount of adverse events for
15 nausea and vomiting, and it seemed to me to be
16 particularly important, from a patient-reported
17 outcome, that in fact they are experiencing this
18 with this particular -- I don't know why. Could
19 you elucidate for me on that issue? Is that
20 reasonable thinking on my part?

21 DR. ROCA: I'm not really sure I can answer
22 that. In the context, I guess you're asking us

1 whether we think that's a reasonable -- it's an
2 interesting question for certain, but I have no way
3 to be able to answer as to whether we think as to
4 the cause of that, and actually I would be very
5 much interested in hearing what the rest of the
6 committee would think about that particular
7 question because it is a very interesting question.

8 DR. LITMAN: That is something we can
9 discuss later this afternoon. Dr. Z?

10 DR. ZACHAROFF: So with respect to the fact
11 that these patients, except in one study, were
12 given general anesthetics, in my opinion, with
13 respect to drowsiness, nausea, vomiting, and other
14 kinds of related adverse effects, unless there was
15 very, very strict control of the general anesthetic
16 agents used, it would be nearly, in my impression,
17 impossible to know whether drowsiness was within
18 the first 6 hours of the general anesthetic, or
19 nausea and vomiting incidents, unless there was
20 premedication for nausea and vomiting. Unless
21 there was use of some agents or in others, it would
22 be impossible, in my mind, to control for that.

1 I'm assuming that the answer is, from the
2 FDA perspective, that we did not keep track of what
3 anesthetic agents were used, and that general
4 anesthesia in and of itself just meant that the
5 patient was asleep for the surgical procedure. Is
6 that a correct assumption?

7 DR. PETIT-SCOTT: So there was a
8 standardized protocol, propofol and an inhalational
9 agent. In terms of actual antiemetic
10 administration during the procedure, I don't have
11 that information readily available, but all
12 patients and all treatment groups within each study
13 received the same general anesthetic.

14 DR. ZACHAROFF: Was there any prohibition of
15 use of narcotic agents during the anesthetic? So
16 if it was an inhalational anesthetic, narcotics
17 were not able to be used as part of the anesthesia?

18 DR. PETIT-SCOTT: There was a limit.

19 DR. ZACHAROFF: There was a limit --

20 DR. PETIT-SCOTT: There was a limit, yes.

21 DR. ZACHAROFF: -- but they were allowed to
22 be used.

1 DR. PETIT-SCOTT: Yes.

2 DR. ZACHAROFF: Okay. Thank you.

3 DR. LITMAN: I have just two hopefully quick
4 questions for the FDA, and I've been given
5 permission to break for lunch early. The first one
6 is Dr. Petit-Scott. The slide that you showed
7 about the comparison of the CKs, the CPKs, it's
8 really common that CKs go up after surgery. Do you
9 know if those results -- and it may be better for
10 the sponsor, if those results were controlled for
11 the type of surgery and/or body weight? Because
12 those are the two things that commonly do affect
13 the CKs.

14 DR. PETIT-SCOTT: The CK data that I
15 reported was only for the PERSIST study, so all
16 those patients underwent a lap chole. In terms of
17 body weight, I don't have that information readily
18 available.

19 DR. LITMAN: Thanks. My second question is
20 more theoretical here. I would like to know from
21 the FDA what you consider to be, in quotes,
22 "long-acting local anesthetic?" One of the things

1 that stuck out at me that was conspicuously absent
2 was that the protocol did not use bupivacaine with
3 epinephrine.

4 In the real world -- and we'll hear from the
5 surgeons hopefully later -- that's our true
6 control. It's pretty unusual we would use plain
7 bupivacaine unless there was some reason not to
8 induce tachycardia or hypertension in the patient.
9 A typical dose of bupivacaine lasts about, I don't
10 know, 4 to 6 hours, and if you add epinephrine to
11 it, it will extend it an hour or so on either end.

12 So can you give us an idea of what we're
13 looking for in a long-acting label and why you did
14 not ask the sponsor to use the usual bupivacaine
15 with epinephrine?

16 DR. ROCA: I'll tackle the second one first
17 with respect to why not use bupivacaine with epi.
18 Partly I think because we're having trouble getting
19 them to use bupivacaine plain, and part of it is I
20 think we may not have necessarily thought that they
21 needed to assess that in order to be able to
22 demonstrate the efficacy and safety of their

1 product. That's number one.

2 With respect to the first question about
3 long acting, I think you're correct in the context
4 that, as you know better than I, the local
5 anesthetics are broken up into ranges, short,
6 medium, and long acting, but those are relative
7 terms. So from our perspective, we don't really
8 have a definition as to what would be considered
9 long acting.

10 If you were thinking in the context of,
11 well, gee, are you going to put something like that
12 in the label? We probably will not put something
13 like long acting. In fact, what we usually do is
14 put the actual amount of time so that you actually
15 see what the time was, partly because you could
16 have something that's long acting, and something
17 later coming on that's longer acting, and something
18 later on coming even longest acting. So from that
19 standpoint, we don't use that terminology; we just
20 give you the time points.

21 DR. LITMAN: Great. Thanks. I'm seeing a
22 note here that lunch won't be ready for a little

1 bit, and we're going to go back to sponsor
2 questions. Is that alright?

3 Oh, I'm sorry. Dr. McAuliffe?

4 DR. McAULIFFE: I just wanted to comment on
5 something that Dr. Z said, and that is the
6 difference between regional and general anesthesia.
7 Because they were not controlled, predetermined
8 general anesthetics, there are different
9 inhalational agents that could affect the
10 postoperative somnolence and not just that you gave
11 opioids, but when you gave opioids.

12 So I'd be giving opioids when the patient is
13 just leaving the room, which is very common when
14 somebody is getting something like Exparel that
15 doesn't have an onset time for quite a while. To
16 give an opioid right prior to leaving the operating
17 room, that certainly could contribute to the
18 immediate post-op nausea and vomiting and
19 somnolence. So without well-controlled prospective
20 studies on the anesthetic, this is all very
21 confounded.

22 DR. LITMAN: Is it okay to go back to some

1 sponsor clarifying questions? Before, some people
2 had their names up, Dr. Horrow, Mr. O'Brien, and
3 Dr. Goudra. Is that still the case?

4 Dr. Horrow?

5 DR. HORROW: I had a clarifying question on
6 slide number 78, please. This is Jay Horrow. The
7 question is, in the upper graph, are the error bars
8 standard deviations or standard errors of the
9 means, and what is the N for each point?

10 DR. VERITY: The N of 5 I recall is the N
11 for these human volunteer subjects. Unfortunately,
12 I'd have to get back to you on the standard error
13 and the standard deviation, which one it is. I
14 just don't recall off the top of my head.

15 DR. HORROW: Thank you. This is a critical
16 issue which I will be discussing later in the
17 discussion time, and we would love to know. Thank
18 you so much.

19 DR. CHOI: Mr. O'Brien, I think you were the
20 next person.

21 MR. O'BRIEN: Thank you. Yes. I have a
22 question. My original question was for Dr. Meisner

1 relative to this issue about adverse events, and
2 particularly as you had indicated in one of your
3 responses to the CNS data that nausea and vomiting
4 is more important to patients, et cetera.

5 So along that line, as I was going through
6 the data, it was very confusing to me, some of the
7 data that was presented in the background material
8 that was given. In this issue of confounding
9 solicited versus unsolicited -- or spontaneous
10 response, when it comes to nausea and vomiting, are
11 those still under that umbrella of confounding
12 data? If someone vomits, does it matter if it's
13 spontaneous or solicited?

14 DR. MEISNER: Can I have the slide up,
15 please? First off, I wanted to point out that this
16 particular graph is taken from the PERSIST trial,
17 and in this case, all of these particular events
18 were specifically solicited because the FDA had
19 requested us to carefully monitor this set of 10
20 particular symptoms, some of which are
21 neurologically related and others may not be.

22 MR. O'BRIEN: I was referring to your

1 slide 71 to 75, not to 99.

2 DR. MEISNER: Oh, I'm sorry. Well, let's
3 see if we can get slide 71 up, please. Yes?

4 MR. O'BRIEN: And I couldn't find a table
5 that showed me the total adverse events for nausea
6 and vomiting for Posimir versus whether it be
7 placebo or bupivacaine.

8 DR. MEISNER: Okay. Can we go back to the
9 slide we were just on, the 2-by-2 slide in the core
10 deck. This one, yes. And can we have the next
11 slide, please?

12 I presented a series of four slides, which
13 we felt was the most informative way to look at
14 adverse events. What we did was we showed you two
15 sets of slides for each comparator group, one being
16 bupivacaine and the other being vehicle control.
17 Then for each of those comparator groups, we
18 separated them into spontaneously collected events
19 and specifically solicited events.

20 So it's important to look at each slide
21 separately or each set of data separately in order
22 to gain a full understanding of what's going on

1 with the drug. If you try to lump them all into
2 one chart, which we unfortunately did in our
3 original submission, you come up with data that's
4 either misleading or not interpretable. In this
5 particular slide, it appears that there is less
6 nausea in the SABER-bupivacaine group than the
7 bupivacaine group, and there's a similar level of
8 vomiting.

9 MR. O'BRIEN: Could we look at slide 74 and
10 75, looking specifically at the placebo group,
11 which is what your intended goal was originally?

12 DR. MEISNER: Sure. Now, don't forget, the
13 placebo group also contained benzyl alcohol, and
14 the FDA has made a claim that many of the various
15 adverse events may be related to benzyl alcohol.
16 But with that said, the incidence of vomiting is
17 slightly higher in the SABER-bupivacaine here than
18 it was in the vehicle-control group, and this is
19 over the full course of the study, which in some
20 studies was 72 hours, and in some studies the
21 collection period for these adverse events was
22 longer. Nausea appeared to be similar for the two

1 groups.

2 MR. O'BRIEN: I guess if I could ask you, as
3 the sponsor, that particular question, was it
4 counterintuitive that you would have more vomiting
5 in the case of the SABER-bupivacaine versus the
6 placebo group? And maybe I hear the point about
7 the original anesthesia, but this is over time --

8 DR. MEISNER: Sure.

9 MR. O'BRIEN: -- it's not over the 6 hours.
10 This is over a 72-hour period. Do you have time
11 data for this data? Did you plot it out over time?

12 DR. MEISNER: I do not have adverse events
13 plotted over time.

14 MR. O'BRIEN: So that being the case then,
15 is it counterintuitive that we would have more
16 vomiting in this than what you would expect in the
17 placebo group that is getting, in fact, some rescue
18 medication?

19 DR. MEISNER: Right. One thing to be aware
20 of is that in this particular comparison between
21 SABER-bupivacaine and SABER placebo or vehicle
22 control, this group included major abdominal

1 surgeries, so that subjects in this group were in
2 house for a long period of time and were being
3 treated with a lot of opioids in both groups.

4 While significant opioid savings were shown
5 in some of our studies, the ones that I
6 specifically presented, there were some larger
7 studies in which the opioid savings were less
8 apparent, if at all, because the patients had pain
9 that resulted both from the incision where the drug
10 was applied and also from manipulation and surgical
11 trauma to the visceral organs. So they had a
12 source of pain that was untreatable by our drug,
13 and therefore had taken possibly as many opioids as
14 the other subjects.

15 MR. O'BRIEN: Last question I guess I have,
16 I didn't see anywhere with any of the material in
17 the FDA or the sponsor side. Was there any
18 patient-reported outcome instruments used for these
19 particular trials, overall summary?

20 I know there were surveys done and solicited
21 data, but was there any patient-reported outcomes
22 overall, like drug liking at the end? Was this

1 worth going through or having it, or were they
2 aware, the patients at any point in time, that in
3 fact they had this versus a placebo, et cetera?

4 DR. MEISNER: Patients were blinded during
5 the entire trial, so they were not aware of which
6 treatment they had. There were some
7 patient-reported outcomes used, but they were all
8 retrospective, and they did not reveal significant
9 differences between groups.

10 MR. O'BRIEN: Okay. Thank you.

11 DR. MEISNER: I would just mention that the
12 one thing that did appear to be quite significant
13 between groups was the use of opioids, which aside
14 from the larger incision surgeries, the reductions
15 were quite dramatic.

16 DR. LITMAN: Just while we're on the
17 subject, what about antiemetics? It's pretty
18 routine here in the states that every patient gets
19 ondansetron or something like it.

20 DR. MEISNER: Sure.

21 DR. LITMAN: Was that controlled for at all?

22 DR. MEISNER: Well, I don't know -- yes. In

1 the PERSIST study for certain, which was probably
2 the most carefully designed study of all the
3 studies, everyone got an antiemetic. It was a 5-HT
4 blocker, basically, a choice of the of the
5 institution.

6 DR. LITMAN: Dr. Goudra?

7 DR. GOUDRA: Basavana Goudra. This question
8 is to Dr. Meisner, if you can open slide 127. You
9 talk about meta-analysis, which shows reduction in
10 comparison to placebo control. I'm sure you guys
11 would have also compared with standard bupivacaine.
12 Do you know, or is it published, or do you know
13 anything about that?

14 DR. MEISNER: Yes. I believe we presented
15 that meta-analysis.

16 DR. GOUDRA: So what did that show in
17 comparison?

18 DR. MEISNER: Let's pull it up if we can,
19 the meta-analysis, the forest plot.

20 This is the forest plot showing five trials
21 that had bupivacaine HCl control arms, which I went
22 to some length to explain were not powered for

1 efficacy and were considered exploratory.
2 Nonetheless, I felt that the data were worth seeing
3 on an exploratory basis.

4 Did you have a question?

5 DR. GOUDRA: The second question --

6 DR. LITMAN: Dr. Goudra, was your first
7 question answered?

8 DR. GOUDRA: Yes.

9 DR. LITMAN: Was that clarified?

10 DR. GOUDRA: It is what it is, yes.

11 DR. LITMAN: Okay.

12 DR. GOUDRA: And the second is, if somebody
13 were to inject it, infiltrate it, either
14 deliberately or accidentally, any idea, based on
15 animal experiments, what would happen to plasma
16 concentrations or toxicity?

17 DR. MEISNER: If the drug were accidentally
18 injected?

19 DR. GOUDRA: Yes.

20 DR. MEISNER: Well first off, I would like
21 to point out that that would be extremely difficult
22 to do given that in almost all cases, there's no

1 needle used to administer the drug. We have not
2 done animal studies in which we injected the drug
3 intravascularly.

4 My presumption, based on our in vitro data,
5 is that the release rate of bupivacaine would
6 certainly be no different than it is when it's
7 sitting in the incision. That release rate is
8 controlled by the depot itself and is fairly well
9 regulated, so one would not expect a burst of
10 bupivacaine in the intravascular space.

11 DR. GOUDRA: Even if the whole 5 cc's are
12 injected -- sorry, infiltrated?

13 DR. MEISNER: Injected intravascularly?

14 DR. GOUDRA: No, infiltration, only
15 infiltration.

16 DR. MEISNER: Well, just to make sure we're
17 using the same terminology, when I think of
18 infiltration, I think of injection into tissue.

19 DR. GOUDRA: Yes.

20 DR. MEISNER: Is that what you're referring
21 to?

22 DR. GOUDRA: Yes.

1 DR. MEISNER: So our drug is not intended
2 for tissue infiltration.

3 DR. GOUDRA: I understand that.

4 DR. MEISNER: Yes. What we have done is
5 we've done trailing subcutaneous injections of our
6 drug because that was initially how we thought it
7 would be administered before we realized it was
8 more effective to administer it directly into the
9 incision, and in those cases, we saw no particular
10 safety issues.

11 In other words, the release of bupivacaine
12 is the same no matter where you put it. The key
13 point is getting it as close to the trauma in the
14 incision as possible to provide the most effective
15 relief. But in terms --

16 DR. GOUDRA: So you don't expect very high
17 plasma concentration if you --

18 DR. MEISNER: Absolutely not. We would
19 expect no higher plasma concentrations than we saw
20 with instillation, and, in fact, some of our PK
21 data is based on subcutaneous injection. So the
22 answer to your question is no.

1 DR. GOUDRA: Thank you.

2 DR. LITMAN: Dr. Zacharoff?

3 DR. ZACHAROFF: Dr. Verity, just to be
4 clear, when you mentioned earlier that there was
5 only one study where anesthetics other than general
6 anesthetics were allowed, for the other studies,
7 with respect to inclusion criteria, patients were
8 selected that could only receive a general
9 anesthetic, and the rationale for that was to avoid
10 super dangerous doses of local anesthetic? Is that
11 correct?

12 DR. MEISNER: If I could respond to your
13 question.

14 DR. ZACHAROFF: Sure.

15 DR. MEISNER: Dr. Meisner.

16 DR. ZACHAROFF: Dr. Meisner. Sorry.

17 DR. MEISNER: Sure. To my knowledge, in all
18 of the trials of SABER-bupivacaine -- and I'd allow
19 Dr. Verity to correct me if I'm wrong -- general
20 anesthesia was the technique used. The reason we
21 didn't allow infiltration of bupivacaine, or
22 regional techniques, or neuraxial techniques is

1 because it would have been impossible to unconfound
2 the data. We wouldn't have known what effects were
3 coming from the bupivacaine that was administered
4 regionally, for example, or the bupivacaine that
5 was coming from our drug.

6 Now, it would have been possible to give
7 everybody a block, but then it's conceivable we
8 wouldn't have seen a pain signal that was large
9 enough to tell whether our drug had a treatment
10 effect. So the default is to go for as little
11 treatment as possible and treat everybody the same,
12 and provide opioids for those who have breakthrough
13 pain.

14 DR. ZACHAROFF: So would the recommendation
15 be then to utilize this drug for postoperative pain
16 management when a general anesthetic is used, or
17 what information could we provide to someone if
18 they choose to do a regional block or a local
19 anesthetic for the surgery, obviously barring the
20 laparoscopic procedures?

21 DR. MEISNER: Sure. That's a great
22 question. We would advise presently that during

1 the first several days after administration of the
2 SABER-bupivacaine that local anesthetic not be
3 administered, and that's only because we don't yet
4 have the data.

5 DR. ZACHAROFF: So the indications for this
6 drug would then be to utilize it for postoperative
7 pain management in patients who receive a general
8 anesthetic.

9 DR. MEISNER: Well, that's up to the FDA. I
10 can't comment on how or how they might not label
11 the drug. But given the fact that regional
12 anesthesia is an important technique, I would
13 rather suspect that there would be quite a bit of
14 postmarketing activity if this drug were to be
15 approved, exploring exactly concomitant use.

16 DR. ZACHAROFF: Okay. Thank you.

17 DR. ZAAFRAN: Sherif Zaafran, kind of
18 following up a little bit to that question. I
19 guess I'm just trying to have a little bit of an
20 understanding because it sounded like the doses of
21 the medication would be high to have it
22 concomitantly done with a regional technique, and I

1 just want to understand, is there any
2 contraindication to utilizing the drug with a
3 regional or neuraxial technique?

4 I guess that's for discussion later on, but
5 it seems like a lot of the side effects that we're
6 talking about, if you did a spinal with no opioids
7 and had the bupivacaine or -- anyway, that's
8 another discussion. But just in general, from the
9 standpoint of contraindication to the use of other
10 techniques, is that there or is it not? Because I
11 kind of heard a little bit differently from the
12 standpoint that the total amount may be of concern,
13 so has that been addressed at all?

14 DR. MEISNER: We believe we've presented
15 data demonstrating the systemic toxicity shown in
16 the trials we've conducted, and it has not been
17 evident; that the plasma levels have not got into
18 the toxic range. We have not studied the
19 co-administration of our drug with a regional
20 technique, so we simply don't have the data to
21 answer that question. Any decisions would be made
22 out of caution rather than data.

1 DR. LITMAN: I'm going to ask a couple of my
2 own questions, please. I just want to get back to
3 the point that Dr. Goudra had asked about. I think
4 it's naive to think that just because the
5 indication for this drug is not to put it into the
6 vein, it's certainly going to happen. I don't
7 agree with you that just because Dr. -- I
8 apologize; I can't remember the surgeon's name who
9 presented with you, that the risk is zero.

10 I work for the Institute for Safe Medication
11 Practices, and I can guarantee you that that will
12 happen. If you don't believe me, you can go to the
13 FDA website, and you can see all -- they've got a
14 wonderful section on all the ways that people have
15 put on the wrong needles, where nurses have put
16 blood pressure cuffs into the IVs and patients have
17 died, and we've connected different drugs to
18 different routes. You know, it's not how we intend
19 to do it, is it? So there's no guarantee that risk
20 is never zero.

21 So with that background in mind, it would be
22 really important for me to not necessarily

1 understand exactly what Dr. Goudra was saying, but
2 our standard of care in anesthesia now is that if
3 someone gets local anesthesia toxicity, or LAST,
4 that you can reverse them with Intralipid.

5 DR. MEISNER: Sure.

6 DR. LITMAN: But you said that you've never
7 injected it into an animal to see that, so can I
8 just assume that you don't know if this drug is
9 reversible with Intralipid?

10 DR. MEISNER: The drug released is
11 bupivacaine.

12 DR. LITMAN: Correct, SABER-bupivacaine.

13 DR. MEISNER: No. SABER-bupivacaine is a
14 formulation that contains the active ingredient
15 bupivacaine. The only difference between
16 bupivacaine HCl and SABER-bupivacaine is that the
17 bupivacaine active component is released more
18 slowly over time than standard plain bupivacaine.
19 Once the bupivacaine is out of the depot, it
20 behaves exactly the same way as bupivacaine given
21 in any other manner.

22 DR. LITMAN: And that would happen if it was

1 in a vein going to the heart?

2 DR. MEISNER: Sure.

3 DR. LITMAN: So there's no reason to suspect
4 that the added ingredients would somehow interfere
5 with the ability to reverse LAST.

6 DR. MEISNER: So LAST would be caused by the
7 bupivacaine that's already come out of the depot;
8 correct? Because while it's in the depot, it's not
9 having an effect on the systemic concentration.

10 DR. LITMAN: Okay. Thank you. One more
11 question is, can you please pull up your slide 79?
12 That's the slide that talks about the differences
13 in blood concentration. I have to say you went
14 through this kind of fast, and I would like this
15 explained a little bit more to my satisfaction.

16 What I'm trying to do, in my confusion
17 between the sponsor and the FDA's data, is figure
18 out blood levels between -- I don't know if this
19 could be brought up, but what I'm looking at on my
20 computer here is the FDA briefing document, which
21 is page 41. I know that refers to different
22 studies.

1 What they're showing here -- and it's really
2 hard to sort out, and I may need the FDA to explain
3 a little bit of this, too -- is there's a figure 1,
4 which is the individual total bupivacaine plasma
5 concentrations following SABER-bupivacaine, the
6 5 mLs. Those units are milligrams per liter, and
7 it's contrasted with figure 2, which is in
8 different units and different kinds of comparisons.
9 Then you're showing this, which shows a completely
10 different story than what was in the FDA briefing.

11 So can you just explain to me, first, where
12 this data came from? These look cumulative.

13 DR. MEISNER: Sure. The data on the left,
14 the blue bars, show the distribution of Cmaxes
15 recorded among all the patients in all the trials
16 in which bupivacaine plasma concentrations were
17 measured. So that's the entire body of data on
18 maximum concentration for SABER-bupivacaine.

19 DR. LITMAN: Okay.

20 DR. MEISNER: So you can see the peak is
21 somewhere around 900 and the tail, it goes to about
22 2400, though there was a single outlier at 2850.

1 It's a little hard to see. It's very small.

2 DR. LITMAN: It is hard to see.

3 DR. MEISNER: But 2850, there was one
4 patient out there.

5 So that's our data. We thought it would be
6 interesting to understand what plasma bupivacaine
7 concentrations develop in clinical practice when
8 people use bupivacaine, typically, infiltrated
9 bupivacaine, regional, neuraxial, et cetera,
10 et cetera. So we did a systematic review of the
11 literature and looked for every paper we could find
12 that talked about plasma bupivacaine concentration,
13 in practice. We compiled all the data from all of
14 those papers, so it's a compilation of data from a
15 systematic review, and plotted all the Cmaxes we
16 can find.

17 The general point is that our Cmaxes are
18 probably not too different from theirs, except
19 there is a long tail in practice that goes into the
20 several thousands, and from our reading of these
21 various reports -- case reports, analyses,
22 meta-analyses -- even these patients did not seem

1 to have toxic events.

2 Now that's not to say that you wouldn't have
3 a toxic event if you got to 5,000. But in our
4 reading of the literature, we saw that there was
5 quite a few more cases where much higher levels of
6 plain bupivacaine -- following plain bupivacaine
7 administration. This slide is telling you that in
8 our clinical trial experience, we haven't gotten
9 anywhere near those levels.

10 DR. LITMAN: I noticed also that your scales
11 are a little bit different in the Y-axis. Why is
12 that? It seems as if they're sort of similar, but
13 they're really not.

14 DR. MEISNER: They're not similar at all.
15 The point here is not the Y-axis, it's the
16 distribution. So one could just as well do these
17 in percentages. In ours, we're showing you the
18 number of subjects. In the other, we're
19 essentially saying, in our compilation of
20 literature reviews, how often did we see Cmaxes at
21 this level.

22 DR. LITMAN: The other question I now have

1 is you talk about an increased risk of LAST, and
2 you had some references. Those references are the
3 papers that have correlated bupivacaine blood
4 levels with local anesthesia toxicity?

5 DR. MEISNER: Yes.

6 DR. LITMAN: In animals or humans?

7 DR. MEISNER: I would point out that the
8 literature in this area is sparse --

9 DR. LITMAN: I know.

10 DR. MEISNER: And that most of the important
11 studies have been done in animals, and in most of
12 those cases, the bupivacaine was intravenously
13 injected at a fairly rapid pace. So typically in
14 the human literature when a case of LAST is
15 reported, the plasma bupivacaine concentration is
16 not co-reported. It's simply an adverse event
17 report or a case report that someone publishes.
18 But they don't stop and take the actual
19 concentration at that time. So doing a real
20 correlation is difficult. This is our best guess,
21 is at somewhere around 3000 or so.

22 DR. LITMAN: And that's based on animal

1 data?

2 DR. MEISNER: That's based on animal data,
3 and I think one or two of these papers is human
4 data. But if you'd like to discuss that further, I
5 would like to have Dr. Gan come up and talk about
6 his clinical experience.

7 DR. LITMAN: TJ, do you know of any human
8 correlation studies?

9 DR. GAN: [Inaudible - off mic].

10 DR. LITMAN: I don't know of any.

11 DR. GAN: TJ Gan. As far as I know, there
12 are really no well-done correlated studies. I
13 think there are a few case reports, and again, in
14 my clinical experience, when you have these toxic
15 events, if you care to measure concentration, there
16 are a few case reports that were really high up,
17 beyond 3[000], 4,000 nanograms.

18 DR. LITMAN: Thanks.

19 It's a couple minutes after 12 o'clock. Are
20 there any -- sure. We have time.

21 DR. HORROW: It's Jay Horrow. I have a
22 clarifying question for Dr. Doraiswamy relating to

1 the comments he made as a clinical investigator in
2 the trial. He commented that he was very pleased
3 with the action of the test substance. My question
4 is when was he unblinded in order to understand
5 what the action was of the results of the test
6 substance versus the comparators? Was this on a
7 case-by-case basis after each one or when was he
8 unblinded?

9 DR. DORAISWAMY: In the first study that I
10 participated in, we kept the patients in house in
11 the research unit, so I did round on the patients
12 for 3 days. In the second PERSIST study, I was
13 completely blinded. I didn't see the patients
14 immediately post-op. I saw them 2 weeks post-op.
15 So it's basically my impression of the data as well
16 as in the first study.

17 DR. HORROW: Jay Horrow. So in the first
18 study, were you unblinded before or after you were
19 making evaluations of the wounds? And if it was
20 after, how long after, and how did you recall the
21 wound appearance?

22 DR. DORAISWAMY: I recall -- just basically

1 I knew who the patient was and I knew that I had
2 given them -- I wasn't the one making the
3 observations or making the assessments. I was just
4 rounding on the patients as a physician, and I knew
5 who got bupivacaine versus study medication.

6 DR. HORROW: Thank you.

7 DR. LITMAN: So wait. So you weren't
8 blinded then?

9 DR. MEISNER: May I clarify? The way we
10 handled this problem in our studies is the surgeon
11 who administered the drug was not blinded, but the
12 evaluator who examined the patient was. So they
13 were independent people.

14 Dr. Doraiswamy may have known which patients
15 had gotten the drug, but he was not the evaluator
16 who was assessing the wound and doing all the other
17 safety evaluations that would have been involved.
18 That was independently done by a blinded
19 individual.

20 Does that make sense?

21 DR. HORROW: Jay Horrow. Does your file
22 indicate the relevant firewalls that were erected

1 in order to obtain --

2 DR. MEISNER: Yes, it does.

3 DR. HORROW: -- appropriate blinding?

4 DR. MEISNER: The firewalls were quite
5 robust, actually.

6 DR. HORROW: Thank you.

7 DR. LITMAN: Dr. Goudra?

8 DR. GOUDRA: Basavana Goudra. Again,
9 getting back to 51 and 52, how could you do a
10 meta-analysis with studies which were so different?
11 And the second, I still don't see a comparison with
12 standard bupivacaine; I only see placebo.

13 DR. MEISNER: Okay. Can we --

14 DR. GOUDRA: 51 and 52, right? Maybe it's
15 somewhere else.

16 DR. MEISNER: Let me pull up slide 363.

17 DR. GOUDRA: 363?

18 DR. MEISNER: Up, please.

19 I didn't show this data during the course of
20 my presentation because we had considered this
21 trial not adequate and well controlled by virtue of
22 the fact that it was prespecified as being

1 exploratory. These were subjects who got
2 laparotomy, which is a major long incision,
3 invasive surgery.

4 DR. GOUDRA: I thought I'm talking about the
5 meta-analysis in 51 and 52.

6 DR. MEISNER: I wanted to make sure you
7 understood -- I'm answering your second question
8 first -- that you wanted to see comparisons of our
9 drug versus bupivacaine HCl. I caution you again,
10 this was exploratory data, but I wanted to make
11 sure that you saw that we had some data that looks
12 rather compelling. It does not say so on the
13 slide, but in fact the comparator was
14 150 milligrams of peri-incisionally infiltrated
15 bupivacaine, which is close to the maximum dose for
16 that use.

17 DR. GOUDRA: Did you say infiltrated?

18 DR. MEISNER: Infiltrated, yes. This was a
19 small trial. You can see the ends are small. It
20 was likely underpowered so that the p-value was
21 non-significant, yet the separation was quite
22 remarkable. So that is one comparison.

1 I'd like to show the next slide, please.
2 This is laparoscopic cholecystectomy also in
3 relation to plain bupivacaine, which shows you
4 pretty good separation between those two curves as
5 well, and this is also 150 milligrams of
6 infiltrated bupivacaine.

7 So we do have data. But just to be sure
8 that it's clear that we did a systematic review of
9 what was adequate and not adequate, we took some
10 data that looked pretty nice and put it in the
11 non-adequate group, and that's why you haven't seen
12 it. But I wanted to make sure, in response to your
13 question, that you saw it.

14 DR. GOUDRA: So if I do understand
15 correctly, there is no meta-analysis which shows
16 that SABER-bupivacaine is better than -- or more
17 effective than standard bupivacaine, contrary to
18 the statement in slide 64.

19 DR. MEISNER: Yes, this meta-analysis --

20 DR. GOUDRA: This compares with --

21 DR. MEISNER: Bupivacaine.

22 DR. GOUDRA: Oh, okay.

1 DR. MEISNER: So this meta-analysis shows
2 you that for all the trials in which there was a
3 comparison with bupivacaine, there was directional
4 improvement in pain with SABER-bupivacaine
5 treatment as compared to bupivacaine HCl.

6 DR. GOUDRA: Again, the groups are not
7 exactly comparable, are they? You have two studies
8 with lap chole.

9 DR. MEISNER: Sure. We're not combining --

10 DR. GOUDRA: You can't call it a
11 meta-analysis.

12 DR. MEISNER: Yes. What we've done is taken
13 all the data we have --

14 DR. GOUDRA: A pooled analysis.

15 DR. MEISNER: -- sure. The green bars
16 represent the primary endpoint data, so that's what
17 was reported in our clinical reports, and the blue
18 diamond represents our not subject level but trial
19 level meta-analysis. So in essence, we averaged
20 the point estimates and confidence intervals for
21 all five of the trials.

22 DR. GOUDRA: Okay. One more question I

1 have is since there is data, even standard
2 bupivacaine 0.5 percent, if it is injected directly
3 say into brachia plexus, it can cause neuronal
4 injury. For example, if this one were to be
5 injected, or infiltrated, can it potentially cause
6 nerve damage in the animal data, since it's very
7 high concentrated?

8 DR. MEISNER: Sure. We have not done any
9 studies looking at regional anesthesia with this
10 product, and we would propose for the time being
11 that it not be recommended for that use.

12 DR. GOUDRA: Well, I wouldn't call it a
13 nerve block; even local-only infiltration.

14 DR. MEISNER: Sure. We have not seen
15 anybody in long-term follow-up who complained of
16 parasthesia or anything you might expect if there
17 were long lasting nerve damage in the vicinity of
18 the administration.

19 DR. GOUDRA: Thank you.

20 DR. LITMAN: One last -- Dr. Horrow, did you
21 have a last question before lunch?

22 (Dr. Horrow gestures no.)

1 DR. LITMAN: Okay. Let's take a break for
2 lunch then. It's 10 after 12, and I apologize, but
3 I'm not going to give you your full hour. We're
4 going to resume back here at 1 p.m. for the open
5 public hearing.

6 Please take any personal belongings you may
7 want with you at this time. Committee members,
8 please remember that there should be no discussion
9 of the meeting during lunch amongst yourselves,
10 with the press, or with any member of the audience.
11 Thank you.

12 (Whereupon, at 12:10 p.m., a lunch recess
13 was taken.)
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A F T E R N O O N S E S S I O N

(1:00 p.m.)

Open Public Hearing

DR. LITMAN: We're going to start with the open public hearing session now. We have three speakers, from what I've heard. The sponsor has asked for a couple minutes after that to clarify some of the issues that were discussed this morning. As long as they are clarifying answers and not new material, then you can have a couple of minutes.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you

1 may have with the sponsor, its product, and if
2 known, its direct competitors. For example, this
3 financial information may include the sponsor's
4 payment of your travel, lodging, or other expenses
5 in connection with your attendance at the meeting.

6 Likewise, FDA encourages you, at the
7 beginning of your statement, to advise the
8 committee if you do not have any such financial
9 relationships. If you choose not to address this
10 issue of financial relationships at the beginning
11 of your statement, it will not preclude you from
12 speaking.

13 The FDA and this committee place great
14 importance on the open public hearing process. The
15 insights and comments provided can help the agency
16 and this committee in their consideration of the
17 issues before them. That said, in many instances
18 and for many topics, there will be a variety of
19 opinions. One of our goals today is for this open
20 public hearing to be conducted in a fair and open
21 way, where every participant is listened to
22 carefully and treated with dignity, courtesy, and

1 respect. Therefore, please speak only when
2 recognized by the chair.

3 Will speaker number 1 please step up to the
4 podium and introduce yourself? Please state your
5 name and your organization you are representing for
6 the record.

7 DR. FOX-RAWLINGS: Thank you for the
8 opportunity to speak today on behalf of the
9 National Center for Health Research. I am
10 Dr. Stephanie Fox-Rawlings, the center's research
11 manager. Our center analyzes scientific and
12 medical data to provide objective health
13 information to patients, health professionals, and
14 policy makers. We do not accept funding from drug
15 or medical device companies, so I have no conflicts
16 of interest.

17 We can all agree that pain relief after
18 surgery is important for patient recovery. Local
19 pain relief that reduces opioid use, reduces
20 adverse events resulting from systemic exposure,
21 and improves recovery would be helpful. However,
22 the evidence presented at this meeting does not

1 demonstrate that SABER-bupivacaine fulfills these
2 goals.

3 Only two of the randomized-controlled
4 clinical trials that tested efficacy had
5 statistically significant reductions in pain
6 compared to placebo. Keep in mind that six other
7 randomized-controlled trials did show greater
8 reductions in pain. The sponsor's briefing
9 materials stated that they define only these two
10 trials that showed benefit as pivotal because their
11 primary endpoint showed a significant benefit. But
12 in fact, pivotal trials should be defined by their
13 intent to demonstrate efficacy and safety, not by
14 their success by demonstrating benefit.

15 It is not clear if there were differences in
16 trials that could explain the differences in
17 results. The drug application method was not the
18 determining factor, nor was the type of surgery.
19 One possible explanation is that the drug has
20 little effect over placebo. Even when the drug was
21 statistically more beneficial than placebo, the
22 benefit was very small and not necessarily

1 clinically meaningful. At best, the difference
2 between drug and placebo was only 1.1 to 1.3 points
3 on an 11-point scale.

4 There are many possible reasons for that
5 difference, differences between health care
6 practices or different selection of patients, just
7 to name two. In addition, the small number of
8 people in some treatment arms or other aspects of
9 trial design could affect the results, making it
10 impossible to be certain that the difference was
11 not due to chance.

12 As I mentioned, the only studies with
13 statistically significant differences were
14 conducted outside the U.S. While the PERSIST
15 trial, which was conducted in the U.S., did not
16 have statistically significant differences in pain,
17 the other studies conducted outside the U.S. also
18 didn't have significant results. Since the FDA's
19 mission is for drugs and devices to be used in the
20 U.S., the lack of efficacy for U.S. patients is a
21 serious shortcoming in the application.

22 It also important that the patients in all

1 of these clinical trials were younger or white,
2 especially those outside the U.S. This is also a
3 serious flaw in the study design unless a sponsor's
4 planning to ask for approval only for younger,
5 white patients.

6 If the drug reduced opioid use and sped
7 recovery, that would be beneficial, however, only
8 one of the two trials that found a significant
9 reduction in pain also had a reduction in opioid
10 use. Neither of the studies have found pain
11 reductions demonstrated faster recovery or improved
12 function.

13 Given the questionable and, at best, small
14 benefit, the FDA raised concerns about the drug
15 safety profile, including effects on nervous system
16 and drug toxicity. Long-term safety is of a
17 particular concern. We have seen cases where a
18 drug can cause long-term adverse events, sometimes
19 in surprising ways.

20 In this case, nonclinical studies indicate
21 that residues can remain in the patient's body for
22 a year, and local adverse events suggest that it

1 affects the tissue where it is applied. The newly
2 supplied analysis and PERSIST trial do not fully
3 address these concerns. We also need to consider
4 that new adverse events may be discovered if it is
5 used in a more diverse population in terms of age,
6 race, or ethnicity.

7 In summary, there's not good evidence that
8 this drug provides a meaningful benefit for
9 patients and certainly not proven that the benefits
10 outweigh the possible risks. More important, the
11 sponsor has not proven that the formulation of the
12 drug works better or is safer than just the opioid
13 bupivacaine.

14 This drug has been on the market for
15 decades, is available as a generic, and does not
16 have these new safety concerns. Plus, there is no
17 reason to approve this drug just to have another
18 tool when there is no evidence that it is a much
19 better tool than currently available options.

20 Thank you for your time.

21 DR. LITMAN: Will speaker number 2 please
22 step up to the podium and introduce yourself?

1 Please state your name and any organization you're
2 representing for the record.

3 MS. BURT: My name is Janice Burt. I do not
4 represent any organization. I have received travel
5 reimbursement from DURECT.

6 In June of 2012, I had a sigmoid colectomy
7 at age 77, and my experience with SABER-bupivacaine
8 was very positive. I realized immediately after
9 waking up from surgery that morphine made me very
10 nauseated, and I resisted using the PCA.

11 When I got up for my first walk after
12 surgery, I followed instructions to use the PCA but
13 quickly regretted it due to the overwhelming
14 nausea. I have no memory of bad pain while in the
15 hospital or after going home. My description would
16 be minor aggravation when moving around. Having
17 this product available for many others would be of
18 great benefit, I believe.

19 DR. LITMAN: Will speaker number 3 please
20 step up to the podium and introduce yourself?
21 Please state your name and any organization you are
22 representing for the record.

1 MS. GUILD: Hello. My name is Nancy Guild,
2 and I am not representing any organization. I
3 would like to disclose that DURECT paid my travel
4 expenses to attend this meeting.

5 In May of the year 2012, I was administered
6 SABER-bupivacaine -- sorry; I was administered the
7 medication prior to undergoing a laparoscopic colon
8 resection surgery.

9 (Laughter.)

10 MS. GUILD: This was given directly to the
11 area where the surgeon would be making his
12 incision. The reason for the surgery was to remove
13 a cancerous tumor that was in my colon. I did not
14 experience any negative side effects or allergic
15 reactions from the medication. This was unusual
16 for me because I am allergic to multiple
17 medications. In fact, I can be a very challenging
18 patient when it comes to managing pain.

19 After being discharged from the hospital
20 7 days later, I experienced some discomfort in the
21 stomach area that was managed for 2 weeks with
22 tramadol. After that, any discomfort was managed

1 with Tylenol. Since that time, I have never
2 experienced any long-term side effects, I have
3 resumed all normal activities, and I am nearly
4 8 years cancer-free. Thank you for letting me
5 speak.

6 **Clarifying Questions (continued)**

7 DR. LITMAN: Thank you.

8 The open public hearing portion of this
9 meeting is now concluded and we will no longer take
10 comments from the audience. The committee will now
11 turn its attention to address the task at hand, the
12 careful consideration of the data before the
13 committee, as well as the public comments.

14 Before I hand it over to Dr. Roca, the
15 sponsor has asked for a couple extra minutes to
16 address some of the clarifying questions on nausea
17 and vomiting. Is that correct?

18 (Dr. Meisner gestures yes.)

19 DR. LITMAN: Please.

20 DR. MEISNER: I'm going to try to keep this
21 very brief. It was apparent to me that there were
22 three issues that there was quite a bit of

1 misunderstanding on, and I'd like to very quickly
2 clarify them.

3 The first one has to do with the question of
4 whether the pain relief that was demonstrated in
5 our efficacy trials was clinically meaningful, and
6 this question has come up several times. Having
7 consulted with our experts on pain trials during
8 lunch, they made me aware that, in fact, there are
9 no meaningful benchmarks to quantify the minimum
10 clinically important difference in the setting of
11 acute pain, specifically acute postoperative pain,
12 so we have to turn to surrogate markers.

13 Slide up, please. Our position is we
14 believe that pain relief is better regardless of
15 how much it is. But if we want to try to make a
16 statement as to whether it's clinically meaningful,
17 the best thing we have to rely on is the use of
18 opioids. In our trials -- in the two pivotal
19 trials, to be clear -- we found that the total dose
20 of opioids taken among patients treated with
21 SABER-bupivacaine was one-third of that in the
22 placebo group.

1 We found -- and this is the hernia trial,
2 just to remind you -- that the time to first use of
3 opioids was significantly delayed, and we found
4 that far fewer patients finished the trial on
5 opioids; in other words, did not go home with an
6 opioid prescription. To us, the point is that if
7 you are using less opioids after surgery, that is
8 proof of the clinical meaningfulness of the pain
9 reduction because we all know that people who use
10 less opioids do it because they have less pain.

11 The second thing I wanted to address is the
12 gentleman up front, Mr. O'Brien, I believe, you had
13 asked a question about nausea and vomiting, which
14 I'm afraid I misunderstood.

15 Slide up, please. You had asked why the
16 incidence of vomiting was greater in the
17 SABER-bupivacaine group than the comparator. You
18 also asked about how vomiting could be a solicited
19 symptom. The reason vomiting is a solicited
20 symptom is that when you assess vomiting, you ask
21 the patient by a questionnaire what happened to
22 them during the day, and the patient may recall

1 that they had some vomiting or they may not. But
2 on the other hand, if you say, "Did you have
3 vomiting today?" they are much more likely to
4 accurately recall that in fact they did have
5 vomiting or they didn't have vomiting.

6 So the most accurate way to assess whether
7 vomiting was increased or not is to actually look
8 at the solicited incidence of vomiting; that is the
9 cases where we said, did you have vomiting today
10 and they answered yes.

11 I've pulled up the slide that shows the
12 solicited incidence of vomiting, and in fact it is
13 somewhat lower in the SABER-bupivacaine group at 5
14 percent versus 8.3 percent, and nausea is also
15 lower at about 15 percent versus 21 percent. On
16 the whole, I would view that as being relatively
17 comparable, but in fact the actual incidence was
18 lower in the SABER-bupivacaine group, and I think
19 that's the most accurate way to look at this
20 question.

21 DR. LITMAN: Clarifying question?

22 MR. O'BRIEN: Could you go to the solicited

1 for the placebo?

2 DR. MEISNER: Sure. Yes?

3 MR. O'BRIEN: In this case, vomiting, in
4 fact both absolutely and percentage-wise, is more
5 with SABER-bupivacaine. That was my question,
6 actually.

7 DR. MEISNER: Yes. In this particular
8 chart, nausea is actually lower in the
9 SABER-bupivacaine group by a small margin and
10 vomiting is marginally increased at 4.7 percent
11 versus 4.2, which to me is not a meaningful
12 difference. So I'm trying to clarify that, in
13 fact, our data do show that the drug either reduces
14 or is comparable in terms of nausea and vomiting in
15 the way that you, I believe, expected it to be if
16 in fact it was doing what we advertised it to do.

17 One last thing, which is that I feel there's
18 been some confusion about the instillation or
19 administration method of the drug, and I just want
20 to emphasize that the drug is designed to be
21 administered with a syringe that has no needle on
22 it, so I just want to make sure. It's simply

1 squirted into the incision. In the early days, we
2 did some experiments where we tried injecting it,
3 but we abandoned those, and we have applied for an
4 indication for simply administering directly into
5 the incision without any needle involved. Thank
6 you.

7 DR. LITMAN: Thank you.

8 DR. LITMAN: Oh, I'm sorry. Dr. Horrow?

9 DR. HORROW: Could I ask a clarifying
10 question on the first part, which was slide 41?

11 DR. LITMAN: Sure. I'll make sure
12 everything gets clear.

13 DR. HORROW: My question about the
14 presentation of this slide is, how did this
15 statistical analysis plan roll out these various
16 comparisons? The primary apparently appears to
17 have a nominal p-value -- I'm sorry, could we have
18 slide 41? Thank you; appears to have a nominal
19 p-value of 0.09, and then there appears to be a
20 secondary analysis with a nominal p-value of 0.023.

21 Were these in a hierarchy? Was there
22 control for multiple comparisons? This is very

1 important in terms of the interpretation of the
2 significance of these particular significance
3 levels.

4 DR. MEISNER: Of course. The secondary
5 opioid-use endpoint, which is shown at the top, was
6 not multiplicity corrected, so it is a nominal p-
7 value.

8 DR. HORROW: So in that case, the primary
9 failed a nominal test at 0.09 being larger than
10 0.05. Therefore, any comparisons beyond that, if
11 it were hierarchical, would be hypothesis-
12 generating alone. So the p-value of 0.023 would be
13 hypothesis-generating and not conclusive. Do you
14 agree?

15 DR. MEISNER: Agreed.

16 DR. HORROW: Thank you.

17 DR. LITMAN: Dr. McCann?

18 DR. McCANN: Mary Ellen McCann. This is for
19 Dr. Meisner. We mentioned, again, you instill it
20 without a needle. Did you test how long of an
21 incision, 5 mLs, is good for?

22 DR. MEISNER: Yes, we did. Yes. We

1 instilled it in small-incision surgery such as
2 laparoscopic and arthroscopic surgery, in which we
3 divided the dose between the various port
4 incisions. We also instilled it in open
5 laparotomy, which had considerably long incisions.

6 DR. McCANN: You don't have a measurement,
7 though?

8 DR. MEISNER: A measurement of?

9 DR. McCANN: Two inches, four inches?

10 DR. MEISNER: Slide up, please. The longest
11 incision we had was 40 centimeters, which is a
12 considerable incision.

13 DR. McCANN: Thank you.

14 DR. LITMAN: How do you administer a
15 teaspoon into 40 centimeters?

16 DR. MEISNER: The technique we used in the
17 long-incision surgeries is we filled the syringe
18 with the 5 cc's and attached an irrigation
19 catheter, which was about as long as the incision.
20 We sewed skin over the catheter, which was
21 positioned at the far end, and injected as the
22 catheter was gradually pulled out of the incision.

1 So that, in essence, it spread across the entire
2 incision as the syringe was being removed.

3 DR. LITMAN: So that's going to be the
4 recommended way that you do this? You'd have to be
5 really slow with your thumb as you're distributing
6 a teaspoon over a large incision, right?

7 DR. MEISNER: It appeared to work pretty
8 well. We didn't have complaints from the
9 investigators. If I could have slide 363, please?
10 Up, please. Just as a reminder, this is the trial
11 in which the drug was administered in that fashion.
12 So it appears that the drug did seem to have its
13 effect in very long incision surgeries, reminding
14 you that this is exploratory data.

15 DR. LITMAN: Dr. Zacharoff?

16 DR. ZACHAROFF: Dr. Meisner, with respect to
17 that technique, we anesthesiologists think about
18 volume that's retained in the tubing and so on and
19 so forth.

20 DR. MEISNER: Sure.

21 DR. ZACHAROFF: So was there something that
22 was used to flush this through?

1 DR. MEISNER: We compensated for the dead
2 space.

3 DR. ZACHAROFF: With?

4 DR. MEISNER: We overfilled the syringe
5 slightly.

6 DR. ZACHAROFF: With?

7 DR. MEISNER: With the drug.

8 DR. ZACHAROFF: Okay, with the drug.

9 DR. MEISNER: Yes. So -- I'm sorry.

10 DR. ZACHAROFF: With more than 5 cc's.

11 DR. MEISNER: Slightly more. There wasn't
12 that much dead space in the irrigation catheter.

13 DR. ZACHAROFF: Okay. But no use of saline
14 or anything like --

15 DR. MEISNER: No.

16 DR. ZACHAROFF: Thank you.

17 DR. LITMAN: While we have the time, are
18 there any other further clarifying questions for
19 the sponsor? Please, Dr. Falta?

20 DR. FALTA: Edward Falta, general surgery.
21 Were the trials controlled for NSAID administration
22 during the surgery and after the surgery?

1 DR. MEISNER: We did not allow and NSAID
2 use, either before or after surgery, during the
3 evaluation period.

4 DR. FALTA: Got you. Then for the hernia
5 trial, were the two arms age-matched? Was there a
6 predominance for young herniorrhaphy patients in
7 one side versus the other or older?

8 DR. MEISNER: Can you bring up the
9 randomization or trial schematics slide from the
10 core deck? We're getting there? Yes, please.

11 The randomization scheme was such that as
12 patients went into the trial, they were randomized
13 to 1 of 4 groups. In theory, the characteristics
14 of the patients' demographics and baseline
15 characteristics should have been spread randomly
16 across all four of the groups. Is that what you
17 wanted to know?

18 (Dr. Falta nods yes.)

19 DR. MEISNER: Okay.

20 DR. FALTA: You don't have the data spread,
21 though, right?

22 DR. MEISNER: I don't have it with me, but I

1 can come up with it if you'd like to see it later.

2 DR. FALTA: One question, just for my own
3 edification, the SAIB component, do you have any
4 data on how that's degraded in the subcutaneous --

5 DR. MEISNER: Yes, absolutely. I'm going to
6 ask Dr. Verity to answer that question.

7 DR. VERITY: Dr. Verity, and I appreciate
8 the question. Basically, SAIB is relatively
9 similar to sucrose. It's broken down through
10 either the Krebs cycle and/or glycolysis. We have
11 done studies in rat to show the degradation and the
12 elimination of SAIB using C-14 SAIB, where the C-14
13 itself is fully labeled across the whole sucrose
14 moiety.

15 If I could, on my previous screen, throw up
16 the ADME slides, the one with the 4 lines on, 552
17 and up. This is the results of C-14-labeled SAIB
18 administered subcutaneously into rats. What we did
19 was then quantitate the level of C-14 that was
20 eliminated from the rat in either urine, feces, or
21 expired air.

22 The line on the top is the total

1 elimination. We did have mass balance in this,
2 where we had 90 percent, actually either residing
3 still in the animal or collected in various
4 collection reservoirs. What you can see, adding up
5 the 3 lower curves, which is the bottom feces, the
6 one in the middle expired air, and the one with the
7 dot is actually urine, you can see that over a
8 6-week period, we get approximately 40 percent or
9 almost 50 percent relative to the actual mass that
10 was calculated in terms of mass balance in this
11 study, eliminated from the rat itself.

12 So most of the remaining stuff was still at
13 the injection site, but I recall and remind you
14 that this is C-14-labeled sucrose, so the label
15 itself could be trapped in local metabolic events
16 at the site of injection.

17 Finally, an important point here to make is
18 since C-14-labeled SAIB was metabolized all the way
19 down to expired CO₂, in other words, elemental
20 carbon, it shows a nice kind of metabolism
21 elimination of the molecule itself.

22 DR. LITMAN: Dr. Zaafran?

1 DR. ZAAFRAN: Yes, thanks. I just wanted to
2 look at slide 41, and after that, slide 46. I'm
3 having a little bit of a hard time understanding
4 why you used the primary opioid-use endpoint as the
5 primary one and not the secondary one because what
6 you have as secondary is the first time you used
7 opioids and the other one is the amount of opioids
8 used after 15 days. To me, that looks like fairly
9 meaningful, the difference between placebo and the
10 different doses there.

11 But with slide 41 and 47, the question I
12 have for you is, is there a control for what
13 narcotic and the amount of narcotic that was used
14 intraoperatively during general surgery,
15 long-acting; short-acting; was it fentanyl; was it
16 morphine; was it dilaudid? Was anything used at
17 all? Was there anything to control for that in
18 both 41 and forty -- I guess it was 47.

19 DR. MEISNER: Sure. There was no control
20 for the use of intraoperative opioid. In some
21 trials, we specifically specified the opioid and in
22 some trials we left it up to institution or

1 anesthesiologist's preference. Regardless of what
2 they used, we simply measured their requests for
3 opioid use when they were made.

4 Is that what you were getting at?

5 DR. ZAAFRAN: It does, just that that data
6 would look so much more meaningful -- I mean, it
7 looks meaningful already, but it would look so much
8 more meaningful if one would understand what opioid
9 they might have had beforehand.

10 Now, in 47, I believe you --

11 DR. MEISNER: Sorry. I just wanted to point
12 something out. Time from study treatment in this
13 study was in hours. So at the tail end, you're
14 looking at 200 hours. Whatever they had in surgery
15 would not have mattered.

16 DR. ZAAFRAN: No, I agree. One wonders
17 about preventative analgesia, whether they would
18 have requested less if they didn't have any pain
19 when they're waking up. But I don't know. That's
20 why I was asking about the controls.

21 DR. MEISNER: Sure.

22 DR. ZAAFRAN: The other interesting thing is

1 that this is only comparing different doses of the
2 SABER-bupivacaine. The other one, which was the
3 arthroscopic decompression, which is I think 47,
4 you didn't have any comparisons so you could
5 compare apples to apples between different doses of
6 SABER-bupivacaine or in the other one, where you're
7 comparing bupivacaine to SABER-bupivacaine.

8 DR. MEISNER: Sure. So this is the other
9 slide.

10 DR. ZAAFRAN: It is, but this is subacromial
11 decompression; the other one was inguinal hernia,
12 right?

13 DR. MEISNER: Correct, yes.

14 DR. ZAAFRAN: So you don't have apples to
15 apples, where you're comparing just bupivacaine to
16 SABER-bupivacaine, for example, in the inguinal
17 hernia, so that you can compare apples to apples
18 with this or different doses of SABER-bupivacaine
19 in the other one.

20 DR. MEISNER: Sure. So the two studies were
21 designed differently, so we don't have those direct
22 comparisons. In both studies, the comparison with

1 bupivacaine HCl itself was not the primary
2 endpoint. It was simply exploratory, and this
3 particular study was there for assay sensitivity.

4 DR. LITMAN: Dr. Shoben?

5 DR. SHOBNEN: Abby Shoben. I appreciate and
6 understand trying to tie clinically meaningful on
7 the pain scale difference to something important
8 like opioid use. Do you have this same data for
9 all the other well-controlled studies as a
10 meta-analysis kind of thing? These are the two
11 that were statistically significant on the pain
12 scale.

13 DR. MEISNER: Sure. Can we put up the
14 opioid meta-analysis, please? Yes, thank you.

15 So this is a forest plot, which shows the
16 overall opioid use for all the trials, and it was
17 all reduction in favor of SABER-bupivacaine
18 treatment, and the overall difference in opioid use
19 did not span the unity line.

20 DR. LITMAN: Dr. Goudra?

21 DR. GOUDRA: Basavana Goudra. What's the
22 maximum recommended dose? Maybe you mentioned it.

1 I missed it.

2 DR. MEISNER: Of our drug?

3 DR. GOUDRA: Yes.

4 DR. MEISNER: The only recommended dose is
5 5 mL.

6 DR. GOUDRA: What would happen if you give
7 more?

8 DR. MEISNER: We've actually done some
9 studies where we did give more. We had several
10 patients who got 7 and a half mL, and we had a fair
11 number of patients who got 7 and a half mL plus
12 another 75 milligrams of bupivacaine.

13 Slide up, please. I think I showed this
14 slide once before. In some of our very early
15 studies, there was a question of whether one might
16 want to give both at the same time. None of the
17 patients in this study showed any evidence of LAST.

18 That's what you wanted to know.

19 DR. GOUDRA: Did it measure the plasma
20 concentration after rating doses?

21 DR. MEISNER: We did, yes.

22 DR. VERITY: As far as PK in terms of plasma

1 curves, with a 7 and a half mL, actually the Cmax
2 really didn't exceed anything greater that we saw
3 with 5 mL. But when you measured the area under
4 the curve, it was dose proportional, linear
5 kinetics, between 2 and a half, 5, and 7 and a half
6 mLs.

7 DR. GOUDRA: Thank you.

8 DR. VERITY: Actually, while I have this
9 slide up, if I can just make one more comment on
10 it. One thing to note is 7 and a half mLs of
11 SABER-bupivacaine is 990 milligrams of bupivacaine
12 base. So in these studies, which we really saw no
13 difference in AE reporting, either incidence or
14 frequency, compared to other studies that had
15 5 mLs, although not a direct comparison because
16 they weren't done at the same time, it's of note
17 that we essentially gave over a gram of bupivacaine
18 to these people, 990 of it released and well
19 controlled by the same metrics, of which 50 mgs or
20 75 mgs was actually bupivacaine hydrochloride given
21 on top at the time of end of surgery.

22 I believe Dr. Z had a question earlier, have

1 you ever done a trial where you've co-administered
2 both be bupivacaine hydrochloride and
3 SABER-bupivacaine. There's actually two trials
4 listed here, and I'll walk you through it because
5 it answers another question that you raised.

6 The first one, CLIN004-001, was a very early
7 hernia trial during the development program, where
8 we were looking at a different route of
9 administration. This was a subcutaneous trailing
10 injection as a paired injection on either side of
11 the incision. So you take the 5 mL dose, divide it
12 into 2 and a half and 2 and a half, and using that
13 trailing injection technique that Dr. Meisner
14 explained for the longer incisions, we applied it
15 here.

16 This patient, or the people in CLIN004,
17 that was how the drug was administered. As part of
18 that study, 45 patients actually had an additional
19 50 milligrams delivered at the time or immediately
20 after when SABER-bupivacaine was administered. The
21 thought at the time -- because literally this was
22 our first trial in hernia -- would be like similar

1 to Exparel, that perhaps the release rate from the
2 depot was not fast enough to cover the first couple
3 hours of pain once the patient's waked up. It
4 turned out there was no difference in pain recovery
5 curves using this subsequently forgotten about
6 route of administration, whether or not we had the
7 additional bupivacaine hydrochloride on or not.

8 The second study, which addresses another
9 one of Dr. Z's questions, is that these patients
10 actually had their hernia operation performed under
11 local anesthesia, so they were not under general
12 anesthesia. So here bupivacaine hydrochloride was
13 given as the local anesthetic, ranging from 75 to
14 100 hundred mgs at the time prior to surgery.
15 Surgery was performed, and then either 5 or 7 and a
16 half mLs of Posimir or SABER-bupivacaine was
17 administered at the close of surgery.

18 So we do have data that suggests from a AE
19 perspective that you can administer a short-acting,
20 local anesthetic along with our Posimir or
21 SABER-bupivacaine formulation. But at this point
22 in time, since this database is relatively small,

1 we would recommend not doing so.

2 DR. LITMAN: Thank you.

3 Jay, you had your name up.

4 DR. HORROW: Jay Horrow. No, it's asked and
5 answered.

6 DR. LITMAN: Thanks. Dr. McAuliffe?

7 DR. McAULIFFE: I just want to follow on the
8 idea of the 5 cc only recommended dose. Would that
9 be the recommended dose if somebody was putting it
10 in around a thoracoscopy, or a chest tube, or
11 something like that, a very small incision, a very
12 vascular area? And if that is the dose, would you
13 also anticipate then the amount of bruising in that
14 area to be the same amount of bruising that we
15 would see in the larger incisions?

16 DR. VERITY: Two answers. We predominantly
17 see bruising on the abdomen, and we have not
18 studied the other surgical procedures that you've
19 mentioned here. With regards to small incisions,
20 you recall that in the lap port or the chole, are
21 they called -- the small port surgeries that we've
22 done, we've actually administered the 5 mL into a

1 very small incision, but equally dividing between
2 the 2 or 3 ports.

3 So we think 2 points; 5 mL goes a long way
4 as evidenced by the long laparotomy surgeries that
5 we've done, but also it's safe to put into a small
6 port, a relatively large volume into a small port.
7 But in particular as to those types of surgeries
8 that you've performed, I don't have any data on
9 that.

10 DR. LITMAN: Dr. Zaafran?

11 DR. ZAAFRAN: Sherif Zaafran. Actually,
12 that kind of prompted me to -- so in the longer
13 incision, is there any reason why you can't dilute
14 this into a larger volume but the same number of
15 milligrams? For example, that 40-centimeter
16 incision, is there a contraindication to dilute it
17 up to 20 cc's, for example, with the same number of
18 milligrams, but to inject that volume over a longer
19 incision?

20 DR. VERITY: So SABER-bupivacaine is
21 hydrophobic and does not mix with water, so you
22 can't dilute it with saline or anything like that.

1 It would just be a blob at the bottom of the
2 syringe, and you would not want to add additional
3 SAIB and benzyl alcohol or other solvents in order
4 to dilute it. So we recommend the 5-mL dose
5 suitable for most incisional sizes that are seen
6 across a variety of surgeries.

7 DR. FALTA: Could you aerosolize that?

8 DR. LITMAN: Sorry, Dr. Falta. Say your
9 name before you speak to get into the record.

10 DR. FALTA: Edward Falta, general surgery.
11 I was just curious if you could aerosolize the
12 applicator.

13 DR. VERITY: Not the current formulation,
14 but we have done other studies with other
15 formulations where you actually can and use that as
16 spray.

17 DR. LITMAN: I have a question. Have you
18 ever looked at the correlation between your blood
19 levels and your pain relief?

20 DR. VERITY: We have, and there's minimal
21 correlation, so the PK/PD relationship really
22 doesn't exist, as with bupivacaine hydrochloride.

1 DR. LITMAN: Yes. It just makes me wonder.
2 I'm still having a hard time envisioning pulling a
3 teaspoon through a large incision and how that
4 could be effective. It just got me thinking maybe
5 it had something to do with blood levels.

6 DR. VERITY: Yes. To follow up on that, all
7 the drug that's measured in the plasma is wasted
8 drug. Where you need the drug is at the site of
9 action and that's the incision. So we use PK as
10 measurements for safety and surrogate measurements
11 for performance of the depot. But the reality is
12 where you need the drug is actually where you put
13 it, and that's in the incision.

14 DR. LITMAN: Any other clarifying questions
15 for the sponsor?

16 DR. VERITY: I could actually clarify one or
17 two more questions from this morning.

18 DR. LITMAN: Sure.

19 DR. VERITY: The gentleman on the end,
20 sorry, asked if it was standard error or standard
21 deviation, and we believe it to be standard error,
22 but knowing that the N is only 5, the standard

1 deviation would be only about twice what you see.

2 DR. HORROW: This is Jay Horrow. Thank you
3 for that clarification.

4 DR. VERITY: One other clarifying point I
5 may offer up is that we do have in our bullpen an
6 expert on pain, who I think might be able to give
7 to the committee, as well as ourselves, a little
8 education on the MCID and/or the clinical relevance
9 of the product.

10 DR. LITMAN: I'm not going to allow that
11 just because it's not an answer to a clarifying
12 question, but thank you.

13 DR. VERITY: Understood.

14 DR. LITMAN: Dr. Roca, you're up. Dr. Roca
15 will now provide us with the charge to the
16 committee.

17 **Charge to the Committee - Rigoberto Roca**

18 DR. ROCA: Thank you. I do appreciate that
19 you've heard quite a bit of information, different
20 studies, different designs, different purposes, and
21 different anatomical sites. I think the comment
22 that was just made a few minutes ago is quite

1 helpful as well in the context that the PK/PD
2 relationship doesn't seem to exist; that the blood
3 plasma levels are primarily used for safety.
4 Therefore, efficacy is really more of a local
5 thing, therefore you think about the fact that the
6 efficacy from one particular site may or may not be
7 extrapolatable to another site. You also heard
8 information regarding some of the safety findings,
9 et cetera.

10 With the first discussion point -- and it's
11 actually a tough question to ask you all, but
12 basically with all the information that you've
13 heard, whether you feel that the applicant has
14 provided sufficient information to support the
15 proposed indication as was read this morning.

16 As you discuss that, that will lead you to
17 the second point, which is whether there are any
18 issues left within this complete response
19 resubmission that still warrant additional studies
20 and to comment on whether you think these could be
21 done before or after approval.

22 When you put all that together, we come to

1 the third discussion point, which is whether the
2 efficacy, safety, and the overall risk-benefit
3 profile -- or the other way you can look at it is
4 whether the efficacy and safety information you've
5 seen results in a favorable risk-benefit profile
6 that will support approval of the application.

7 As we've done before, we end up with a
8 voting question where we're asking you whether you
9 recommend approval of the product as noted there
10 for the proposed indication, and as you've done
11 before, if you voted yes, your rationale and
12 whether you feel that any post-approval study
13 should be required. Similarly if you voted no, to
14 discuss your rationale, and particularly at that
15 point whether additional data are needed for
16 approval.

17 I know it is a big task, and I appreciate,
18 and I'm looking forward to the discussion. Thank
19 you.

20 **Questions to the Committee and Discussion**

21 DR. LITMAN: Thank you, Dr. Roca.

22 We will now proceed with the questions of

1 the committee and panel discussions. I would like
2 to remind public observers that while this meeting
3 is open for public observation, public attendees
4 may not participate except at the specific request
5 of the panel.

6 Can I please have discussion question 1?
7 Please discuss whether the applicant has provided
8 sufficient information to support the proposed
9 indication. As always, put your name tags up, and
10 we'll keep a running tally and try to get you one
11 by one.

12 Dr. Zaafran?

13 DR. ZAAFRAN: Thanks. Sherif Zaafran. The
14 one bit of information that most supports the
15 answer to this question is the time to the use of
16 the first opioid. In those two studies, one with
17 the inguinal hernia and the other one with the
18 subacromial decompression, there is a marked
19 difference.

20 The only thing that I hesitate with is not
21 knowing what was given during the general
22 anesthetic. So if there was a suggestion that I

1 would have that would clarify that, it would be
2 that you can't do it with a subacromial
3 decompression, but at least with the inguinal
4 hernia -- or with those, to actually control it
5 using a neuraxial technique where you're not
6 getting any type of narcotic whatsoever and to look
7 at the comparisons of the first-dose narcotic.
8 Then you're really kind of taking away all the
9 other confounding bias that might be there.

10 It would also answer the other question
11 about all the other adverse events, the nausea, the
12 vomiting, the somnolence, all the other stuff,
13 which could be confounded by all the different
14 types of general anesthetic medications that you're
15 giving.

16 You're taking all of that away and you're
17 normalizing it to just numbing half the body and
18 figuring out is that one medication causing or
19 allowing or affecting a longer period of time for
20 the first dose of opioid to be given. That would
21 give me a much stronger feeling that this
22 medication is working as indicated.

1 DR. LITMAN: Dr. Higgins?

2 DR. HIGGINS: Jennifer Higgins. I agree. I
3 do think that the applicant has provided sufficient
4 information. I'm going to go a little further than
5 that and ask the FDA a question about what would be
6 permissible postmarketing in terms of study. I'm
7 imagining that comparative studies would not be
8 permissible postmarketing, enrichment studies to
9 focus on some of the safety concerns. What is
10 permissible?

11 DR. ROCA: Definitely if there are any
12 questions regarding a safety issue that you would
13 like to have cleared up, identified, you can
14 certainly do that. I'm trying to figure out
15 whether an efficacy study, per se, would fall into
16 that category. I know that we're thinking that
17 sometimes that would be beneficial, particularly if
18 you're trying to assess efficacy also in view of
19 safety concerns.

20 So you're trying to weigh both so that you
21 end up actually requesting not a safety study, per
22 se, as you would imagine a safety study would be

1 designed and powered, et cetera, looking just for
2 safety findings, but an efficacy study that would
3 also be looking at safety but putting into context
4 the efficacy.

5 So to a certain extent, the kind of studies
6 that would be allowed or permitted in the
7 post-approval stage would be depending on what
8 questions the committee thinks would be useful to
9 try to address.

10 DR. HIGGINS: Thank you.

11 DR. LITMAN: Dr. Horrow?

12 DR. HORROW: Jay Horrow. The proposed
13 indication does not include any time scale on it.
14 Given the likelihood that the clinical trials
15 section of the label will show data out to
16 72 hours, I believe that consideration of the
17 duration of action of the product is under
18 discussion. From a scientific perspective, I'm
19 struggling with visual issues of data transparency
20 both on the part of the sponsor and the FDA.

21 The sponsor in slides 39, 40, 45 and 46
22 presents data with standard errors of the mean

1 rather than standard deviations. Most critical
2 journals insist that data be presented graphically
3 with standard deviations rather than standard
4 errors of the mean. They also provide lines that
5 connect the dots even though there are no data for
6 those connecting lines. All we have are data at
7 the time periods.

8 The agency presents only the lines, not even
9 the dots, and no errors whatsoever, and that makes
10 it very difficult for panel members to understand
11 and to evaluate the data; although the FDA, I
12 believe, correctly identifies and calls into
13 question any effect that might occur beyond
14 12 hours.

15 Visually to the person looking at these
16 graphs -- and by the way, the FDA slides in
17 question are 19, 23, 32, and 33. To the person
18 viewing these graphs, we focus on the area under
19 the curve and any differences between those areas,
20 although it's unclear whether this is a correct
21 outcome variable to assess whether or not the test
22 substance actually is a long-acting anesthetic. It

1 gives, in my impression, an incorrect visual
2 impression of what we should be getting out of the
3 data.

4 An unbiased evaluation of the data at time
5 points greater than 12 hours, showing absolute mean
6 differences with 95 percent confidence intervals
7 and with or without nominal p-values, would be
8 appropriate. As we know, even though those curves
9 look like they are separate beyond 12 hours, we
10 know from the FDA, who has tested those points,
11 that in fact there is no difference, but visually
12 it looks like that. The sponsor repeatedly said
13 visually you can see a difference, but we know that
14 we can be tricked visually. We need to see the
15 data and the nominal p-values.

16 Now, the meta-analysis itself has separate
17 issues relating to that. I saw no measures in the
18 meta-analysis of heterogeneity, no chi-squares, for
19 any of the curves that were presented. There's
20 dubious rigor for the meta-analyses, and I'll be
21 happy to discuss the meta-analyses separately when
22 we consider discussion point number 3. But I'm

1 just struggling as somebody looking at the data to
2 come away with a proper interpretation. Thank you.

3 DR. LITMAN: Thank you. Dr. Zacharoff?

4 DR. ZACHAROFF: Hi. Kevin Zacharoff. With
5 respect to this question, the sufficient
6 information, I would agree with everything
7 Dr. Zaafran said, first of all, which made me not
8 have anything to say. But then with respect to
9 what we heard just a few minutes ago, for the first
10 time this technique for long incisions about
11 withdrawing a catheter and squirting as you
12 withdraw, I have no image of what I would use or
13 where I would go in the operating room to get a
14 line tubing or what kind of catheter I would use;
15 whether it would look like a surgeon's drain that I
16 would infuse this through as I was pulling it out.
17 So I'd have to say that I was not provided
18 sufficient information about this, quote/unquote,
19 "long incision withdrawal technique." Thank you.

20 DR. LITMAN: Dr. Goudra?

21 DR. GOUDRA: Basavana Goudra. In spite of
22 all of the limitations so elegantly described by

1 Dr. Horrow, especially in connection with the
2 meta-analysis, having published all 10
3 meta-analyses myself, I don't even think that this
4 will fit the definition of meta-analysis. But in
5 spite of everything, I think the applicant has
6 demonstrated its benefits, at least when it's
7 compared with the placebo. That's the FDA
8 requirement. I think they've done the job that's
9 required.

10 DR. LITMAN: Dr. McAuliffe?

11 DR. McAULIFFE: I'm looking at the question
12 to support the proposed indication, which I am
13 assuming is postoperative incision. The orthopedic
14 case was a closed orthopedic case and not an open
15 shoulder, and the open shoulders, as we know, are
16 the most painful orthopedic cases, in the shoulder
17 region anyway. So I don't know that it does give
18 us enough confidence that they've provided
19 sufficient information, for at least every proposed
20 indication. Thank you.

21 DR. LITMAN: Dr. Cullen?

22 DR. CULLEN: I just want to make a comment

1 on what was just spoken about. I agree with
2 Dr. Zacharoff. As a surgeon, I can't get my head
3 around how you would do that, and I'm the guy doing
4 that. I don't know why it's just placed on the
5 wound and close the skin over, so that catheter
6 thing doesn't make much sense.

7 What I would like to have seen, which was
8 just touched on, was the shoulder operations. I'm
9 not an orthopedic surgeon, but those patients have
10 a level of pain preoperatively, and it would have
11 been nice in the shoulder segment of their studies
12 to see what their pain scores were prior to the
13 operation, because I think that might have an
14 effect.

15 Finally, I keep on looking at the slides, I
16 think it's 39 and those other ones. The initial
17 effect of this medication is in the first 12 to 18
18 hours, it looks like. After that, I just
19 can't -- to me, it doesn't suggest that it's
20 working for 72 hours.

21 DR. LITMAN: Dr. Shoben? Sorry. You're too
22 close.

1 DR. SHOBNEN: Sorry. Abby Shoben. I just
2 wanted to say that I think I really agree with the
3 FDA's characterization that it's a modest, at best,
4 and inconsistent effect. If you look at -- you're
5 not seeing sort of the same -- what you would like
6 to see ideally is a consistent, similar effect
7 across a variety of surgical sites with this sort
8 of nice, what they were powered for, 1-ish point
9 difference supported by the opioid-use data being
10 in favor of the new drug, and you just don't see
11 that. There are just so many trials where you see
12 smaller effects and very modest benefits, and
13 that's really problematic to me in terms of
14 supporting this indication.

15 DR. LITMAN: To sum up, I think I heard that
16 we needed more information in general about the
17 anesthetic regimens to properly put the comparisons
18 into proper context. I heard that some people felt
19 that there were very significant limitations of the
20 data interpretation, based on varying visual
21 analyses that were tough to interpret.

22 We as the ADCOM, I feel like we're sort of

1 caught in this weird place here today, where we
2 came in looking at the FDA briefing booklet, and
3 the sponsor presented an awful lot of additional
4 data. Almost both sides had a lot of cumulative
5 data, and it was really difficult to understand
6 what all that cumulative data meant. It seemed
7 that at times each side kind of used the cumulative
8 data to support their interpretations.

9 I do agree with Dr. Horrow about the
10 meta-analysis, and I'd go one step further
11 that -- I can tell you as a journal editor and
12 frequent reviewer, meta-analyses are one of the
13 most common articles that we get to review, and the
14 heterogeneity is so frustrating, and I don't think
15 they're appropriate for FDA approval.

16 I also heard limitations on interpretation
17 of technical methodologies such as the instillation
18 method, but on the other hand, I also heard some
19 opinions that thought that they did provide
20 sufficient information to support this specific
21 proposed indication.

22 Did I capture everything?

1 (No audible response.)

2 DR. LITMAN: Question 2, please. Discuss
3 whether there are issues with this complete
4 response resubmission that warrant additional
5 studies and, if so, should these studies be
6 conducted before or after approval? Dr. Zeltzer?

7 DR. ZELTZER: Lonnie Zeltzer. I think it
8 was in the requested -- I can't remember whether
9 you had discussed it here or whether it was in the
10 materials of what was requested. But while there
11 is no IV indication, as was mentioned, in the OR
12 you can see lots of risks that are unintended, like
13 something being given IV when it shouldn't or a
14 very bloody area and something happens. We don't
15 have any preclinical data on risks if this were in
16 this amount and width, its adjuvant, if it's given
17 IV, and that's a concern in terms of potential
18 unintended consequences and risks.

19 DR. CHOI: Dr. Zacharoff?

20 DR. ZACHAROFF: Hi. Kevin Zacharoff. With
21 respect to this discussion point, as we already
22 discussed with respect to question 1, additional

1 studies, possibly after approval, that control more
2 for the use of intraoperative analgesic
3 administration that allow for a greater level of
4 comfort with respect to regional anesthetic
5 techniques, et cetera, et cetera, I think could be
6 very valuable.

7 I did hear loud and clear the idea about
8 really not having a good sense about what the
9 demographics of these patient populations were, and
10 it's really hard for me to say when I think of
11 inguinal hernia patients or certain other types of
12 common surgical cases, that I have an image in my
13 mind of some age groups, but I think that that
14 could be beneficial as well.

15 Given that this is a fixed-dose medication
16 based on volume, it's entirely possible that there
17 could be some patient populations where what we
18 would consider to be a high dose could end up being
19 a super high dose. So again, I think that that
20 could be conducted after approval. Thank you.

21 DR. LITMAN: Dr. Goudra?

22 DR. GOUDRA: Basavana Goudra. The only

1 post-approval study I would certainly recommend is
2 in animals if given intravenously, whatever the
3 dose, to see whether Intralipid is effective to
4 treat it, because there will really be a day when
5 some of us are going to inject intravenous
6 accidentally, and there's no debate about it. All
7 kinds of stuff has been injected, including by
8 myself. Thank you.

9 DR. LITMAN: Dr. McAuliffe, did you have a
10 question?

11 DR. McAULIFFE: I do. I think that we're
12 making some assumptions that the postoperative
13 drowsiness and somnolence is related perhaps to the
14 anesthetic or the opioids that are given. We don't
15 know that. And it could be related to the benzyl
16 alcohol. So I think that a study needs to be done
17 to determine what's causing this. What scale are
18 we using to measure somnolence? It was sort of
19 dismissed a little bit that it was a false
20 positive; that it was solicited versus
21 self-reported.

22 How does a patient who's in the recovery

1 room tell you I'm drowsy? That's a self-report.
2 So I think we need to kind of have a scale and find
3 out exactly what it is, and then figure out what's
4 causing it.

5 DR. LITMAN: Dr. McCann?

6 DR. McCANN: Mary Ellen McCann. I don't
7 know whether testing should be done before or
8 after, but I have issues, like everybody else, with
9 the vehicle of administration. I think if this
10 were a single-use spray, that it would be hard to
11 misuse it. I think you put a syringe in the hands
12 of doctors or nurses, it's just going to get used
13 incorrectly at some point, and it could have tragic
14 results when that was done. If it were a spray and
15 it worked, I think it would be much, much safer.

16 DR. LITMAN: What about prepackaging it with
17 a 5-cc syringe only attached to some kind of an
18 applicator that Dr. Zacharoff or Dr. Cullen was
19 talking about, of some sort?

20 DR. McCANN: I think that would be a step in
21 the right direction.

22 DR. LITMAN: Dr. Zaafran?

1 DR. ZAAFRAN: Sheriv Zaafran. I just want
2 us to also be careful that we're holding folks to
3 the same standard as what we do in the operating
4 room right now. We routinely draw up local
5 anesthetics in syringes and inject it into
6 tissue -- or surgeons do of course --
7 intraoperatively, routinely. Is there a risk that
8 it could be injected intravascularly? Yeah. When
9 you're locally infiltrating into tissue, that's
10 probably a little bit higher risk as opposed to
11 just kind of dropping it onto the wound.

12 Now, I think there may be some value in a
13 bloody site where there could potentially be some
14 absorption there and what the risk of that might
15 be. But if you're talking about an incision that
16 you're closing -- I don't really know of many
17 surgeons who'd be closing an incision that's very
18 bloody. That's one of the things that you guys
19 worry about and watch out for all the time. So I'm
20 not sure I'd worry about that as much because it's
21 not very different from what we do already today on
22 a routine basis.

1 DR. LITMAN: Dr. Falta?

2 DR. FALTA: Edward Falta, general surgery.

3 I think one of the things that confounds the
4 postoperative symptoms is that they're mixing
5 visceral surgery with somatic surgery and testing a
6 somatic analgesic. I thought maybe postmarketing
7 or post-approval, studies would be kind of more
8 specific for a somatic surgery, like a
9 hemorrhoidectomy, or umbilical hernia, or like a
10 burn debridement, something that doesn't involve
11 visceral surgery.

12 DR. LITMAN: Mary Ellen, do you still --

13 DR. McCANN: Well, to your point, we don't
14 ordinarily put 660 milligrams of bupivacaine in a
15 syringe. I think that's where the danger comes in,
16 even more so.

17 DR. LITMAN: Any other comments about
18 question 2?

19 (No response.)

20 DR. LITMAN: In sum, I think I heard a
21 couple of different themes here. One was some
22 concern about how to put the comparisons and the

1 results in context; one based on demographics and
2 the other one, which is I think an important point,
3 that the studies were mixed. Not all pain is the
4 same and not all pain responds to local anesthetics
5 in the same way.

6 The other theme I heard here was that there
7 would be some need for some further studies to
8 better define the risk. I definitely agree with
9 Dr. Goudra that even though there is no theoretical
10 reason why the treatment of local anesthetic
11 toxicity wouldn't be appropriate, I can't imagine
12 you just can't take two dogs and make sure you can
13 rescue them; just not labs.

14 (Laughter.)

15 DR. LITMAN: What's causing the somnolence?
16 In further studies on the instillation, one of the
17 things I think some of us agree on is that in all
18 the studies that were done, there must have been so
19 many variety of ways that the drug was put into the
20 wound, whether it's the 40 centimeters dragging
21 method or the laparoscopic method which, again, if
22 you're doing a cholecystectomy, how many holes do

1 you have guys, 3, usually 4? How do you put a
2 teaspoon into four different holes? I know. I see
3 these every day, and I can't even imagine. So I
4 think those things need to be further defined.

5 Did I capture everybody's --

6 (No response.)

7 DR. LITMAN: -- okay, question 3, please.

8 Discuss whether the efficacy, safety, and overall
9 risk-benefit profile of Posimir support the
10 approval of this application. Here now we're
11 talking about just overall risk-benefit, your
12 impressions.

13 Dr. McCann? In doubt?

14 DR. McCANN: No, I forgot to put it down,
15 but I just did do the division, and maybe I did it
16 wrong. But if you were comparing it with
17 0.25 percent bupivacaine, it's equivalent to
18 264 mLs. I mean, that's a lot.

19 DR. LITMAN: Dr. Cullen?

20 DR. CULLEN: Joe Cullen, surgery. One thing
21 that the FDA presented, we looked at headache and
22 nausea and vomiting. If you look at those

1 percentages, I not only thought they were not
2 statistically significant between the different
3 medications, but I didn't think they were
4 clinically significant either.

5 Having said that, I still think that first
6 12 to 24 hours that you see the difference in the
7 drug, a lot of that could be due to the anesthetic
8 that was given and what was given during the
9 anesthetic, especially in the first 12 hours. So I
10 think it's a safe medication. I don't think these
11 differences we see in the patient groups are
12 significant both statistically and clinically.

13 DR. LITMAN: Dr. Horrow?

14 DR. HORROW: Jay Horrow. I'm still
15 struggling to convince myself on the efficacy part,
16 and of course if we're not convinced of efficacy,
17 there's no reason to even discuss safety.

18 Understandably, this product was designed to be
19 long-acting, so the efficacy studies contained a
20 primary outcome variable that should show that
21 effect, namely the area under the curve from 1 to
22 72 hours, I believe, with the hope that 72 hours

1 would be the duration of effect.

2 However, when we look at the individual time
3 point data, we scratch our heads about whether
4 we're seeing an effect much beyond 12 hours. And
5 I, for one, question seriously drawing straight
6 lines in between 2 data points and believing that
7 there's a linear effect there.

8 As we know, there are certain thresholds for
9 drug concentrations for effect, and if that
10 threshold is breached, then the effect wears off.
11 So even if the amount of drug is going down
12 linearly, that doesn't mean the effect of that drug
13 is linear; so I struggle with that.

14 That then leads us to the sponsor's argument
15 of looking at not necessarily the pain scores that
16 we see in those data points, but the time to first
17 opioid use as rescue as an outcome variable, which
18 it wasn't. It was a secondary variable, and that
19 then raises the question of whether the data could
20 be -- whether another study could be done with that
21 as the outcome, the primary outcome variable
22 submitted as evidence of efficacy.

1 Suffice to say, looking at the Kaplan-Meier
2 curves, there are very few events for opioid
3 requests beyond 16 hours, and I'm referring to
4 slide 48 of the sponsor's presentation. And I
5 believe it's those Kaplan-Meier curves that are the
6 correct ones to present and not the forest plots
7 for meta-analyses that we were shown.

8 That makes me think that, in fact, what's
9 happened here is it doesn't matter what you got in
10 terms of pain relief, after a certain period of
11 time, most people don't feel pain anyway, or at
12 least not enough to require an opioid. So that
13 raises the question as to whether you even need, in
14 the models studied, a long-acting local anesthetic.

15 So I'm struggling to understand the efficacy
16 here. If I can't get my arms around the efficacy,
17 then I certainly can't evaluate benefit-risk when
18 it comes to any of the safety issues. Thank you.

19 DR. LITMAN: Dr. Zacharoff?

20 DR. ZACHAROFF: Hi. Kevin Zacharoff. With
21 respect to this question, probably my biggest
22 concern with respect to the overall risk-benefit

1 profile was the post-procedural contusion issue.
2 If Dr. Cullen gave this to a patient in the
3 operating room and then is being covered by me, and
4 I'm seeing the patient 2 days later, and I see
5 this, if I haven't received the proper amount of
6 education, I might think there's a hematoma
7 developing.

8 I haven't seen a photograph of what this
9 post-procedural contusion was, but I did hear
10 descriptions about size and the palm of my hand. I
11 would imagine that with a relatively small
12 incision, but yet post-procedural contusion that
13 might persist for up to 30 days, that I might be
14 concerned, and that concerns me from the safety and
15 risk perspective.

16 With respect to the other issues, I think in
17 a real world, what we've already heard said, and I
18 would just reinforce, is that I would be gauging
19 its efficacy based on the amount of opioid that
20 somebody needed to be administered before, what
21 Dr. Gan spoke about very much earlier today, and
22 has recovery after surgery. That is something that

1 is intended to get patients out the door relatively
2 quickly with relatively few complaints.

3 I think that whether we're talking about the
4 first 24 hours or the 24-to-72 hour period,
5 Dr. Horrow, you might be absolutely right, that it
6 might not make that much of a difference. But what
7 was different was that the patient didn't require a
8 lot of narcotic. There wasn't some amount of
9 period of time that they needed to be observed
10 after they got a dose of narcotic, and they were
11 able to get out the door and be on this enhanced
12 recovery track.

13 So if I take it all into perspective and
14 don't necessarily worry as much about what the
15 potential for intravenous injection might be, even
16 though I do agree with that as a post-approval
17 study -- this is not a case where an
18 anesthesiologist is going to pick up a syringe with
19 a clear solution in it and accidentally inject it
20 intravenously. This is a situation where a surgeon
21 who scrubbed is going to be administered this drug
22 that is likely delivered to them by the scrub

1 technician, who will have received it from the
2 scrub circulating nurse in the operating room, and
3 there should be enough checks and balances in place
4 to make sure that the right medication is getting
5 delivered without a needle into the right location.

6 If this was an anesthesiologist injected
7 drug, I think the risk of intravenous injection
8 might actually be higher, to be honest with you,
9 and we all know how labeling syringes and
10 abbreviating terms and things like that could
11 happen. So post-procedural contusion is the thing
12 that concerns me the most here, and the educational
13 challenges from a safety perspective is what
14 concerns me the most. Thank you.

15 DR. LITMAN: Dr. Zaafran?

16 DR. ZAAFRAN: Sherif Zaafran. I don't know
17 if there's enough to suggest that it's equally
18 efficacious in the long term or as a long-acting,
19 but there does seem to be enough evidence to show
20 that it is better than the current or similar local
21 anesthetics in the short term. So when I think of
22 C-sections, for example, where you could apply it

1 over the wound, or when you look at, again,
2 inguinal hernias or others, where these are
3 surgical center patients, just looking at the data,
4 it looks like you could get these patients out of
5 the surgery center without having to give them any
6 opioids, that to me is fairly meaningful.

7 So from the standpoint of efficacy -- and I
8 heard from the FDA earlier that they would more
9 than likely in the labeling put down a specific
10 time period as opposed to, say, a long-acting,
11 short-acting, whatever, which wouldn't really mean
12 much. But it is fairly meaningful that the number
13 of hours before you give an opioid is significantly
14 longer, at least looking at that one inguinal
15 hernia study, and even the other one. Even though
16 you're not comparing it directly to bupivacaine, I
17 would, if it potentially gets approved in the
18 post-period, re-look at general anesthetics versus
19 neuraxial anesthetics and see if those adverse
20 events would actually be significantly less.

21 I think the way it is right now, it's
22 probably just as much. I think if you took a

1 general anesthetic patient, in general, without
2 anything at all, you probably may see those exact
3 same numbers. The question is that if you didn't
4 have to administer general anesthetic, would it be
5 any higher than somebody who didn't receive
6 anything at all except for 12.75 milligrams of
7 bupivacaine intrathecally.

8 So from that standpoint, I think the safety
9 and the overall risk-benefit profile is not any
10 higher. There's not any additional risk except for
11 the contusion standpoint. But efficacious, I think
12 it is in the short term, and it is something that
13 seems to be better than at least bupivacaine by
14 itself.

15 DR. LITMAN: Dr. Higgins?

16 DR. HIGGINS: Jennifer Higgins. I feel
17 comfortable with the risk-benefit profile, and
18 there are some modest safety concerns, the
19 contusions. Some of the CNS, I don't mean to make
20 light of those, they're very significant, but do
21 feel like that could be surveilled postmarketing.
22 I like the fact that it's an opioid-sparing

1 medication, and we don't come across many of those.
2 And I really appreciate the fact that the sponsor
3 took the time to enroll folks who are above the
4 general age cutoff and up to age 87, which makes me
5 feel more comfortable for the older adult
6 population as well.

7 DR. LITMAN: Dr. McAuliffe?

8 DR. McAULIFFE: I too am worried a little
9 bit about the postoperative bruising, and 90
10 percent of the patients had a postoperative
11 bruising that could be as big as a man's hand, and
12 I think that's fairly significant. I think that
13 does interfere with the matrix of the tissue. It
14 predisposes potentially to postoperative infection.
15 And I'm worried about certain subgroups of
16 patients, patients with cancer, or patients who are
17 prone to infection with diabetes. So we don't
18 really know that that's more of a problem than what
19 we're just kind of seeing here.

20 DR. LITMAN: Dr. Horrow? Did you -- no.
21 Dr. Shoben?

22 DR. SHO BEN: Abby Shoben. I want to echo

1 Dr. Horrow's comments in terms of -- my concern
2 here is really with the efficacy. I don't really
3 see the level of efficacy that some of you seem to
4 be seeing. If you look at PERSIST, which was the
5 trial that was done as part of the complete
6 response rate, Part 1, where they were looking at
7 saline placebo, you see -- this is in a lot of
8 places, but it's on FDA slide 30. You have this
9 mean difference of 0.8 compared to the placebo
10 control, and that didn't reach statistical
11 significance. Then the comparison with
12 bupivacaine, where it was powered to look for a
13 difference with just plain bupivacaine, you see a
14 difference at 0.3, which is clearly not
15 statistically or clinically meaningful.

16 So really, I'm struggling with the efficacy
17 part here. Because I'm struggling so much with the
18 efficacy, what would otherwise be minor safety
19 concerns about the bruising and some of the minor
20 signals of bleeding, it just becomes a little bit
21 more magnified because there's so little efficacy.

22 DR. LITMAN: Before I sum up, I'll add my

1 own opinion. I think that taking into
2 consideration the risk, I'm not that concerned with
3 the contusions and some of the minor things. My
4 most important concern is theoretical, as
5 Dr. McCann alluded to before, putting
6 660 milligrams of bupivacaine with the potential
7 for intravascular injection. The problem is that
8 it hasn't happened, and there's no way that we here
9 today can define what that risk is.

10 As I mentioned before, I feel pretty
11 confident in saying that it will happen eventually,
12 but does that mean that that should tip the
13 balance? Everyone's going to have to have their
14 own opinion here as to whether or not that's
15 significant enough to compensate for the benefits.
16 The benefits, it was really hard to tell what the
17 benefits were here today. We've heard so much
18 different data from both sides, much of which was
19 cumulative and in many different types of patient
20 populations and anesthetic conditions.

21 If you think about what we're doing now,
22 which is bupivacaine in most of my cases -- I'll

1 confirm with the surgeons who use bupivacaine with
2 epi or plain -- we're getting about 6 to 10 hours
3 maybe. That's probably exaggerating; probably 4 to
4 8 is my best guess. Anything beyond 8 hours -- I
5 don't care about 72; anything beyond 8 would be a
6 big improvement over what's on the market right
7 now, at least for a local, and, if we could, avoid
8 opioids for a few days or even NSAIDs.

9 So I think the risk-benefit ratio, honestly,
10 it's really hard to tell. I don't have a really
11 good grasp. The only thing I will say is this
12 drug, the original NDA was 2006? You would think
13 we'd know by now. That's the thing that keeps
14 nagging at me. So those are my personal views
15 here.

16 So to sum up, I heard a mixed opinion. I
17 heard some people are very concerned about the
18 contusions. I heard a couple of different things
19 about the benefits. Some people were satisfied
20 with the benefits, and they thought that there was
21 a favorable benefit-to-risk ratio, while other
22 people, like myself, Dr. Horrow, could not evaluate

1 it properly in the context of the data that was
2 presented. So it's a really difficult choice.
3 It's a really difficult equation to try and come up
4 with on one side or the other, and I think that's
5 what we're hearing, is a gestalt of what I'm
6 getting.

7 Did I leave anything out? Anybody else?

8 (No response.)

9 DR. LITMAN: So where's my script? Here we
10 go.

11 So we never took a break. Nope? Is
12 everybody okay without a break? Does anybody need
13 a break? Can we take 5 minutes for people to run
14 to the bathroom and back before we go with the
15 voting? Is that alright? Thank you.

16 How about this? We'll take 9 minutes. It's
17 2:21. Please come back at 2:30.

18 (Whereupon, at 2:21 p.m., a recess was
19 taken.)

20 DR. LITMAN: It's 2:30. It looks like
21 everybody's back.

22 We will be using an electronic voting system

1 for this meeting. Once we begin the vote, the
2 buttons will start flashing and will continue to
3 flash even after you have entered your vote.
4 Please press the button firmly that corresponds to
5 your vote. If you are unsure of your vote or if
6 you wish to change your vote, you may press the
7 corresponding button until the vote is closed.
8 After everyone has completed their vote, the vote
9 will be locked in.

10 The vote will then be displayed on the
11 screen. The DFO, Moon, will read the vote from the
12 screen into the record. Next, we will go around
13 the room and each individual who voted will state
14 their name and vote into the record. You can also
15 state the reason why you voted as you did if you
16 want to. We will continue in the same manner until
17 all questions have been answered or discussed.

18 Question 4, which is the vote, do you
19 recommend approval of Posimir bupivacaine
20 extended-release solution, 660 milligrams per 5 mL
21 or 132 milligrams per mL, for the proposed
22 indication of single-dose instillation into the

1 surgical site to produce postsurgical analgesia?

2 Are there any questions about that question;
3 any concerns or --

4 (No response.)

5 DR. LITMAN: -- okay. Just to clarify
6 because I know this will come up. It says
7 "extended release," and we don't know what that
8 means, essentially.

9 A, If you voted yes, please discuss the
10 rationale for your vote and specify whether any
11 post-approval studies should be required. If you
12 voted no, please discuss the rationale for your
13 vote and what additional data are needed for
14 approval.

15 Are there any clarifying questions before
16 the vote?

17 (No response.)

18 DR. LITMAN: Okay. Please press the button
19 on your microphone that corresponds to your vote.
20 You have approximately 20 seconds to vote. Press
21 the button firmly. After you have made your
22 selection, the light may continue to flash. If you

1 are unsure of your vote or if you wish to change
2 your vote, please press the corresponding button
3 again before the vote is closed. When everyone has
4 voted, we will be signaled that the vote is
5 complete, and we will reveal the votes.

6 (Voting.)

7 DR. LITMAN: The vote is complete.

8 DR. CHOI: We have 6 yes, 6 no, zero
9 abstentions.

10 DR. LITMAN: Now that the vote is complete,
11 we will go around the table and have everyone who
12 voted state their name, vote, and if you want to,
13 you can state the reason why you voted as you did
14 into the record.

15 Moon, is it possible to put up the A and the
16 B choices again so the panelists can see what the
17 FDA is interested in? No, we can't. Okay. So
18 hopefully everybody remembered. If you stated yes,
19 did you want further studies? Was that what it
20 was?

21 Dr. Roca, would you mind reading that again
22 just so we're clear? Oh, actually I have it. I

1 apologize. I got it right here.

2 If you voted yes, please discuss the
3 rationale for your vote and specify whether any
4 post-approval studies should be required. If you
5 voted no, discuss the rationale for your vote and
6 what additional data you would want for approval.
7 So we'll start with Dr. McCann.

8 DR. McCANN: I voted no. I was convinced by
9 what Dr. Shoben and Dr. Horrow said. The safety
10 issues were definitely there for me as well, but
11 mostly I was concerned that they really didn't
12 demonstrate efficacy. Further studies that
13 demonstrate efficacy would be useful in the future
14 for me to vote yes.

15 DR. ZACHAROFF: Hi. Kevin Zacharoff. I
16 voted yes for pretty much what we've discussed with
17 the last four discussion points. My yes has the
18 asterisk about doing post-approval studies
19 regarding intravenous administration in animal
20 testing to see if it can be reversed by Intralipid.
21 My yes is also qualified by some type of packaging
22 that would include a delivery device that would

1 enable somebody to administer this withdrawal
2 administration without leaving it up to everybody's
3 own ingenuity. Thank you.

4 DR. McAULIFFE: Maura McAuliffe. I voted no
5 based both on limited time demonstration of
6 efficacy in the more invasive surgeries, especially
7 orthopedic surgeries, and also reliance on post hoc
8 analysis for explaining potential safety risks with
9 respect to wounds and to neurological events that
10 were measured. What could be done? Prospective,
11 well-designed, well-controlled studies to look at
12 those factors and demonstrate that they aren't
13 safety risks.

14 DR. ZELTZER: Hi. Lonnie Zeltzer. I voted
15 no. Mostly, I wasn't convinced of efficacy beyond
16 12 hours from the data presented. I still think
17 that it would behoove the company to have an
18 administration package for consistency of
19 administration before it gets approved rather than
20 hoping it will all work out afterwards. From a
21 safety standpoint, I'd like to know what happens if
22 IV, this amount comes into the intravenous system

1 and can it be reversible.

2 DR. GOUDRA: Basavana Goudra. I voted yes.

3 The reason being it's not a magic bullet, we all
4 know that. Such a thing probably doesn't exist.

5 It's certainly better than placebo and probably
6 better than standard bupivacaine, at least in some
7 situations, some procedures. The contusion, or
8 whatever, the swelling, I think it's minor.

9 Accidental IV is my biggest concern, and I should
10 know whether I'm going to put this patient on a
11 cardiopulmonary bypass machine or I'm going to give
12 it a shot with Intralipid. So that certainly needs
13 to be done. But other than that, I think this drug
14 should be ready to go.

15 DR. LITMAN: This is Ron Litman, and I voted
16 no. This was a tough decision. I felt conflicted
17 and confused from the beginning of the meeting
18 because the data that was presented by the sponsor
19 was not reflective of what I had prepared for this
20 meeting, so I really didn't know how to adequately
21 assess their benefit data. I can't assess their
22 risk data because the most important risk for me is

1 the accidental injection, and I don't know how to
2 assess that. It's just a feeling. So when it all
3 came down to it, I would love for this drug to
4 work.

5 As I mentioned before, anything that extends
6 post-op numbness, anesthesia beyond 6 or 7 hours,
7 would be a huge improvement; not just incremental,
8 it would be huge. Overall, I just felt that the
9 risks outweighed the benefits based on what I heard
10 today, but that may not be the case. If the FDA
11 ends up approving this, I would ask you to be very
12 careful in the kinds of clinical studies you
13 portray on the label because that will determine
14 what the marketing says.

15 So I don't think the marketing will say
16 long-lasting or extended release. It's going to
17 say effective up to such and such hours, and
18 obviously that's constrained by what's on the
19 label, and that's what you guys determine.

20 DR. SHO BEN: Abby Shoben. I voted no. I
21 think I've expressed my efficacy concerns pretty
22 earlier. It was a tough decision because I do

1 think if you made me bet, I would say it is
2 probably very slightly better than placebo, but the
3 concern is that very slightly better than placebo
4 coupled with some potentially relatively minor
5 safety concerns makes that benefit-to-risk
6 calculation really challenging.

7 I do think that the response the sponsor had
8 looking at the PERSIST data and looking at the
9 safety relative to bupivacaine, and doing the
10 stratified analysis looking at solicited versus
11 spontaneous reporting was really helpful in terms
12 of really clarifying the safety issues. But in the
13 end, with such a minor efficacy signal, even
14 remaining minor safety concerns was what pushed me
15 toward a no vote.

16 DR. HIGGINS: Jennifer Higgins. I voted yes
17 for many of the reasons already stated. I think
18 it's a promising opioid-sparing product, and I like
19 the fact that it provides a new option for people,
20 such as the woman who spoke in the public hearing
21 session with an allergy to certain medications.

22 With respect to postmarketing exploration, I

1 would say continued safety monitoring, obviously,
2 and then mitigation of some confounding variables
3 such as surgical procedures, and then the
4 anesthetics that have been discussed today, too.

5 MR. O'BRIEN: Joe O'Brien, and I would say
6 it's probably the most difficult decision that I
7 made voting yes, and I voted it because I was
8 conflicted, I was confused, I was concerned. I
9 think that when I read through all the materials
10 and then listened to it, I had a sense that it was
11 fake it until you make it. I thought that the data
12 was inconsistent, and there are some unknowns that
13 I don't understand that don't seem to make sense
14 with the rationale that I heard and that I saw.

15 As a patient who's had subtotal colectomies
16 and 6 spine surgeries, I am very concerned for
17 adverse events like for vomiting and nausea. While
18 they may be short-term, they are very important to
19 the patient that's there, and I just don't
20 understand what I'm seeing, and it still doesn't
21 make sense to me. In the process, it's explained
22 with data -- I don't want to say manipulation, but

1 data movement -- in favor of something, and I just
2 don't see the efficacy. I don't think it's strong
3 that's there.

4 So despite all those concerns, at the end of
5 the day, we do have a need for opioid-sparing
6 medications. On top of the fact that this is a
7 medication that's going to be driven by clinicians,
8 anesthesiologists, and surgeons in the operating
9 room, I let that be a level of safety for me to
10 say, okay, let them take it there, but it is the
11 most conflicting vote I've ever made.

12 DR. ZAAFRAN: Sherif Zaafran. I voted yes.
13 One of the things I would say about the
14 postoperative period is I think pain scores are
15 relatively useless, and I worry that we're spending
16 so much time focusing on that from a standpoint of
17 efficacy. When you look at the decision by the
18 patient to ask for their first dose of opioid
19 medication, clearly being different with this
20 medication compared to others, that to me is a
21 stronger point of efficacy that I would look at in
22 the postoperative period.

1 There's a vast difference. A point score of
2 1 or 2, I've seen people who have a score of 2 and
3 want medication and people that have a score of 8
4 who don't want anything. So what does that mean?
5 If you're not needing opioid medications and you're
6 not asking for it, to me that's more meaningful
7 because at the end of the day, what are we trying
8 to do here? We're trying to minimize the use of
9 opioids in the postoperative period, and hopefully
10 that translates into less opioids in the longer
11 term afterwards. That to me is more meaningful.

12 From the side effect standpoint, again, I'm
13 not sure I see much of a difference from a general
14 anesthetic with nothing versus with the medication,
15 so it would be helpful afterwards to see that bias
16 removed, whether by doing neuraxial blocks and
17 using the medication with that; that would give a
18 much clear indication.

19 The one caveat, I think we should have the
20 intravascular studies on non-Labrador dogs, but
21 that would also be helpful just to give a clearer
22 picture from that standpoint.

1 DR. CULLEN: Joe Cullen. I agree with
2 everybody that questioned the efficacy, including
3 the FDA. That's why I voted no. I do think it's
4 safe, however, the recent discussion regarding
5 bruising, the data on that was very vague, and
6 bruising is kind of a vague thing, so I think that
7 that data needs to be teased out. I do think it's
8 safe, however, I do have some concerns about the
9 bruising issue.

10 DR. FALTA: Edward Falta. I voted yes. I
11 felt that the first 24 hours was a great utility
12 for an analgesic, and I agree with Dr. Zaafran with
13 not requesting opioids in the first 24 hours is a
14 very strong indicator of efficacy. I also think
15 that you need a more consistent delivery vehicle
16 than the catheter. I think a spray would probably
17 be more consistent and safer. I also think that we
18 need a postmarketing study comparing the standard
19 practice with bupivacaine and epinephrine injection
20 versus the application of this product.

21 DR. LITMAN: Thank you.

22 Dr. Horrow, even though you weren't voting,

1 do you have any last minute comments or
2 editorializations for us, for the FDA?

3 DR. HORROW: Jay Horrow. I would say that
4 despite the completely split 50/50 vote, thanks to
5 the talents of our chairman, who conducted an
6 excellent meeting, sufficient information has come
7 from the participants of the panel, the sponsor,
8 and the FDA to provide valuable information to the
9 FDA to see a way forward that this drug might
10 achieve approval someday. Thank you.

11 DR. LITMAN: Thank you.

12 Dr. Roca, any final comments before we
13 adjourn, now that this is all clear?

14 DR. ROCA: I think I mentioned, when I gave
15 the charge to committee, that the question was
16 simple and straightforward, but the response
17 obviously is not. I certainly appreciate all the
18 discussion. It's obvious that you guys really
19 thought about it, and some of you, as you
20 mentioned, have really wrestled with it. I
21 certainly understand that, and I do appreciate your
22 time and your effort, and I wish everybody a safe

1 trip home.

2 **Adjournment**

3 DR. LITMAN: Thank you. We kindly ask that
4 all attendings dispose of any trash or recycling in
5 the proper receptacles in the hallway and not leave
6 any waste items on the floor or tables.

7 Panel members, please remember to take all
8 your personal belongings with you as the room is
9 cleared at the end of the meeting day. Please
10 leave your name badge on the table so that may be
11 recycled. All other meeting materials left on the
12 table will be disposed of. We will now adjourn the
13 meeting. Thank you.

14 (Whereupon, at 2:46 p.m., the meeting was
15 adjourned.)

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