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

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Moon Hee V. Choi, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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C O N T E N T S

FDA Presentations

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

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

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

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

DR. ROCA: Good morning. My name is Rigo

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

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

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

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

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

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

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

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

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

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

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

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

DR. SHOBEN: Hi. I'm Abby Shoben. I'm an associate professor of biostatistics at The Ohio State University.

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

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

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

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

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

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

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

DR. LITMAN: Thanks, everybody.

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

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

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

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

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

Conflict of Interest Statement

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

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

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

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

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

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

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

Today's agenda involves discussion of new

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

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

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

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

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

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

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

DR. LITMAN: Thanks, Moon.

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

FDA Introductory Remarks - Rigoberto Roca

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. LITMAN: Thanks, Rigo.

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

understand the context of an individual's presentation.

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

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

We will now proceed with DURECT Corporation's presentation.

Applicant Presentation - Neil Verity

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

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

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

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

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

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

Applicant Presentation - Tong Gan

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Applicant Presentation - Neil Verity

DR. VERITY: Thank you, Dr. Gan.

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

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

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

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

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

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

anatomic spaces under visual guidance if desired.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

While the Tmax varies along a continuum from

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

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

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

the SABER-bupivacaine safety profile.

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

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

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

Reduced opioid use and delayed time to first

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

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

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

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

Applicant Presentation - Jon Meisner

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

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

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

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

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

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

We developed this response to deal with the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The primary evaluation period for

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

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

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

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

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

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

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

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

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

the placebo group at only 2.7 hours.

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

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

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

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

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

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

were women.

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

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

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

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

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

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

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

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

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

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

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

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

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

Now, the next question is how do we know the

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

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

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

conclusions that can be drawn from these data.

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

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

Let me sum up the data in support of

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

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

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

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

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

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

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

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

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

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

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

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

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

I'm going to show you a series of four

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

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

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

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

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

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

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

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

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

On the left of this slide is a plot of the distribution of maximum plasma concentration seen in every subject in the clinical program who was exposed to SABER-bupivacaine. The highest Cmax observed was 2850 nanograms per mL in a single subject undergoing laparoscopically assisted colectomy, which fell short of the point at which

the risk of LAST begins to increase.

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

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

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

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

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

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

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

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

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

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

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

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

characterizations of the SABER-bupivacaine safety profile.

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

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

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

correlation with plasma bupivacaine concentration.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

potential complications one at a time.

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

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

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

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

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

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

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

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

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

SABER-bupivacaine in clinical trials.

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

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

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

mild or moderate in severity.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

surrounding tissues.

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

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

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

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

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

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

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

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

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

At the beginning of our presentation, we

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

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

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

Applicant Presentation - Asok Doraiswamy

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

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

First, the method of administration is a

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

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

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

any bruising.

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

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

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

Applicant Presentation - Harold Minkowitz

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

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

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

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

Clarifying Questions

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

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

Dr. Zacharoff?

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

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

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

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

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

DR. ZACHAROFF: Okay. Thank you.

DR. LITMAN: Dr. Zaafran?

DR. ZAAFRAN: Thanks. Sherif Zaafran. This

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. LITMAN: Dr. McCann?

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

DR. MEISNER: Sure.

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

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

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

DR. MEISNER: Sure.

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

DR. MEISNER: Right.

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

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

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

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

We then sent that in to the FDA, noting the

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

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

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

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

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

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

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

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

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

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

DR. McCANN: Thank you.

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

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

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

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

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

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

DR. HIGGINS: So no pronounced AE phenomenon.

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

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

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

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

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

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

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

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

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

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

FDA Presentation - Renee Petit-Scott

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

An overview of the FDA presentation is

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

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

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

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

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

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

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

I will now discuss the clinical development program for Posimir. The applicant's proposed language for the indication is as follows. "Posimir is an extended-release solution of bupivacaine, an amide local anesthetic, indicated for single-dose instillation into the surgical site to produce postsurgical analgesia." The indication during the initial NDA review cycle was for broad postsurgical analgesia as well, but was worded slightly differently.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

treatment arms.

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

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

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

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

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

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

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

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

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

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

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

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

This table shows the results of

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

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

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

bupivacaine 75 milligrams.

The anticipated difference was 0.8 units from mean pain on movement for 0 to 48 hours, the primary endpoint in PERSIST Part 2. Mean pain for 0 to 72 hours was a secondary endpoint and is shown here for consistency to all the other studies. PERSIST Part 2 did not show a statistically significant difference for mean pain on movement for either of the plan time frames.

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

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

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

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

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

bupivacaine arm to address later advice from FDA. The role of this study is not agreed upon.

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

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

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

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

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

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

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

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

FDA Presentation - Renee Petit-Scott

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

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

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

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

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

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

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

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

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

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

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

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

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

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

While the regulatory threshold for approval

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

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

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

analyses.

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

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

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

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

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

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

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

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

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

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

A blinded radiologist re-read baseline and

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

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

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

the next slide.

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

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

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

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

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

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

variables, to comprehensively evaluate shoulder joint function.

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

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

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

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

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

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

and all resolved without treatment.

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

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

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

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

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

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

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

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

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

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

for all treatment groups.

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

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

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

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

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

less impressive on study day 29.

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

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

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

between treatment groups by study day 29.

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

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

Moving on to a brief discussion of the

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

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

In general, review of this information from

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

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

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

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

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

In conclusion, while the ongoing safety

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

Clarifying Questions

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

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

(No response.)

DR. LITMAN: There are no clarifying

questions for the FDA?

(No response.)

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

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

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

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

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

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

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

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

DR. ZACHAROFF: One more question. Ms.

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

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

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

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

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

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

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

DR. LITMAN: Thanks. Dr. Horrow?

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

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

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

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

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

you look at differences in the later time points?

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

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

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

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

DR. HORROW: Thank you.

DR. LITMAN: Dr. Shoben?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. PETIT-SCOTT: There was a limit.

DR. ZACHAROFF: There was a limit --

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

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

DR. PETIT-SCOTT: Yes.

DR. ZACHAROFF: Okay. Thank you.

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

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

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

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

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

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

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

product. That's number one.

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

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

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

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

Oh, I'm sorry. Dr. McAuliffe?

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

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

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

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

Dr. Horrow?

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

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

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

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

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

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

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

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

MR. O'BRIEN: I was referring to your

slide 71 to 75, not to 99.

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

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

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

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

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

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

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

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

groups.

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

DR. MEISNER: Sure.

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

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

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

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

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

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

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

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

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

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

MR. O'BRIEN: Okay. Thank you.

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

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

DR. MEISNER: Sure.

DR. LITMAN: Was that controlled for at all?

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

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

DR. LITMAN: Dr. Goudra?

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

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

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

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

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

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

Did you have a question?

DR. GOUDRA: The second question --

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

DR. GOUDRA: Yes.

DR. LITMAN: Was that clarified?

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

DR. LITMAN: Okay.

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

DR. MEISNER: If the drug were accidentally injected?

DR. GOUDRA: Yes.

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

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

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

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

DR. MEISNER: Injected intravascularly?

DR. GOUDRA: No, infiltration, only infiltration.

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

DR. GOUDRA: Yes.

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

DR. GOUDRA: Yes.

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

DR. GOUDRA: I understand that.

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

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

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

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

DR. GOUDRA: Thank you.

DR. LITMAN: Dr. Zacharoff?

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

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

DR. ZACHAROFF: Sure.

DR. MEISNER: Dr. Meisner.

DR. ZACHAROFF: Dr. Meisner. Sorry.

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

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

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

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

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

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

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

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

DR. ZACHAROFF: Okay. Thank you.

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

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

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

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

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

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

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

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

DR. MEISNER: Sure.

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

DR. MEISNER: The drug released is bupivacaine.

DR. LITMAN: Correct, SABER-bupivacaine.

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

DR. LITMAN: And that would happen if it was

in a vein going to the heart?

DR. MEISNER: Sure.

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

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

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

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

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

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

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

DR. LITMAN: Okay.

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

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

DR. LITMAN: It is hard to see.

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

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

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

to have toxic events.

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

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

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

DR. LITMAN: The other question I now have

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

DR. MEISNER: Yes.

DR. LITMAN: In animals or humans?

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

DR. LITMAN: I know.

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

DR. LITMAN: And that's based on animal

data?

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

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

DR. GAN: [Inaudible - off mic].

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

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

DR. LITMAN: Thanks.

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

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

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

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

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

DR. DORAISWAMY: I recall -- just basically

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

DR. HORROW: Thank you.

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

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

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

Does that make sense?

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

in order to obtain --

DR. MEISNER: Yes, it does.

DR. HORROW: -- appropriate blinding?

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

DR. HORROW: Thank you.

DR. LITMAN: Dr. Goudra?

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

DR. MEISNER: Okay. Can we --

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

DR. MEISNER: Let me pull up slide 363.

DR. GOUDRA: 363?

DR. MEISNER: Up, please.

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

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

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

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

DR. GOUDRA: Did you say infiltrated?

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

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

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

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

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

DR. GOUDRA: This compares with --

DR. MEISNER: Bupivacaine.

DR. GOUDRA: Oh, okay.

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

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

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

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

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

DR. GOUDRA: A pooled analysis.

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

DR. GOUDRA: Okay. One more question I

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

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

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

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

DR. GOUDRA: Thank you.

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

(Dr. Horrow gestures no.)

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

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

(Whereupon, at 12:10 p.m., a lunch recess was taken.)

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

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

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

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

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

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

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

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

demonstrate that SABER-bupivacaine fulfills these goals.

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

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

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

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

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

It also important that the patients in all

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(Laughter.)

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

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

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

Clarifying Questions (continued)

DR. LITMAN: Thank you.

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

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

(Dr. Meisner gestures yes.)

DR. LITMAN: Please.

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

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

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

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

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

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

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

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

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

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

DR. LITMAN: Clarifying question?

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

for the placebo?

DR. MEISNER: Sure. Yes?

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

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

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

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

DR. LITMAN: Thank you.

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

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

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

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

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

important in terms of the interpretation of the significance of these particular significance levels.

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

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

DR. MEISNER: Agreed.

DR. HORROW: Thank you.

DR. LITMAN: Dr. McCann?

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

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

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

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

DR. MEISNER: A measurement of?

DR. McCANN: Two inches, four inches?

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

DR. McCANN: Thank you.

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

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

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

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

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

DR. LITMAN: Dr. Zacharoff?

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

DR. MEISNER: Sure.

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

DR. MEISNER: We compensated for the dead space.

DR. ZACHAROFF: With?

DR. MEISNER: We overfilled the syringe slightly.

DR. ZACHAROFF: With?

DR. MEISNER: With the drug.

DR. ZACHAROFF: Okay, with the drug.

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

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

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

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

DR. MEISNER: No.

DR. ZACHAROFF: Thank you.

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

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

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

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

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

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

(Dr. Falta nods yes.)

DR. MEISNER: Okay.

DR. FALTA: You don't have the data spread, though, right?

DR. MEISNER: I don't have it with me, but I

can come up with it if you'd like to see it later.

DR. FALTA: One question, just for my own edification, the SAIB component, do you have any data on how that's degraded in the subcutaneous --

DR. MEISNER: Yes, absolutely. I'm going to ask Dr. Verity to answer that question.

DR. VERITY: Dr. Verity, and I appreciate the question. Basically, SAIB is relatively similar to sucrose. It's broken down through either the Krebs cycle and/or glycolysis. We have done studies in rat to show the degradation and the elimination of SAIB using C-14 SAIB, where the C-14 itself is fully labeled across the whole sucrose moiety.

If I could, on my previous screen, throw up the ADME slides, the one with the 4 lines on, 552 and up. This is the results of C-14-labeled SAIB administered subcutaneously into rats. What we did was then quantitate the level of C-14 that was eliminated from the rat in either urine, feces, or expired air.

The line on the top is the total

elimination. We did have mass balance in this, where we had 90 percent, actually either residing still in the animal or collected in various collection reservoirs. What you can see, adding up the 3 lower curves, which is the bottom feces, the one in the middle expired air, and the one with the dot is actually urine, you can see that over a 6-week period, we get approximately 40 percent or almost 50 percent relative to the actual mass that was calculated in terms of mass balance in this study, eliminated from the rat itself.

So most of the remaining stuff was still at the injection site, but I recall and remind you that this is C-14-labeled sucrose, so the label itself could be trapped in local metabolic events at the site of injection.

Finally, an important point here to make is since C-14-labeled SAIB was metabolized all the way down to expired CO2, in other words, elemental carbon, it shows a nice kind of metabolism elimination of the molecule itself.

DR. LITMAN: Dr. Zaafran?

DR. ZAAFRAN: Yes, thanks. I just wanted to look at slide 41, and after that, slide 46. I'm having a little bit of a hard time understanding why you used the primary opioid-use endpoint as the primary one and not the secondary one because what you have as secondary is the first time you used opioids and the other one is the amount of opioids used after 15 days. To me, that looks like fairly meaningful, the difference between placebo and the different doses there.

But with slide 41 and 47, the question I have for you is, is there a control for what narcotic and the amount of narcotic that was used intraoperatively during general surgery, long-acting; short-acting; was it fentanyl; was it morphine; was it dilaudid? Was anything used at all? Was there anything to control for that in both 41 and forty -- I guess it was 47.

DR. MEISNER: Sure. There was no control for the use of intraoperative opioid. In some trials, we specifically specified the opioid and in some trials we left it up to institution or

anesthesiologist's preference. Regardless of what they used, we simply measured their requests for opioid use when they were made.

Is that what you were getting at?

DR. ZAAFRAN: It does, just that that data would look so much more meaningful -- I mean, it looks meaningful already, but it would look so much more meaningful if one would understand what opioid they might have had beforehand.

Now, in 47, I believe you --

DR. MEISNER: Sorry. I just wanted to point something out. Time from study treatment in this study was in hours. So at the tail end, you're looking at 200 hours. Whatever they had in surgery would not have mattered.

DR. ZAAFRAN: No, I agree. One wonders about preventative analgesia, whether they would have requested less if they didn't have any pain when they're waking up. But I don't know. That's why I was asking about the controls.

DR. MEISNER: Sure.

DR. ZAAFRAN: The other interesting thing is

that this is only comparing different doses of the SABER-bupivacaine. The other one, which was the arthroscopic decompression, which is I think 47, you didn't have any comparisons so you could compare apples to apples between different doses of SABER-bupivacaine or in the other one, where you're comparing bupivacaine to SABER-bupivacaine.

DR. MEISNER: Sure. So this is the other slide.

DR. ZAAFRAN: It is, but this is subacromial decompression; the other one was inguinal hernia, right?

DR. MEISNER: Correct, yes.

DR. ZAAFRAN: So you don't have apples to apples, where you're comparing just bupivacaine to SABER-bupivacaine, for example, in the inguinal hernia, so that you can compare apples to apples with this or different doses of SABER-bupivacaine in the other one.

DR. MEISNER: Sure. So the two studies were designed differently, so we don't have those direct comparisons. In both studies, the comparison with

bupivacaine HCl itself was not the primary endpoint. It was simply exploratory, and this particular study was there for assay sensitivity.

DR. LITMAN: Dr. Shoben?

DR. SHOBEN: Abby Shoben. I appreciate and understand trying to tie clinically meaningful on the pain scale difference to something important like opioid use. Do you have this same data for all the other well-controlled studies as a meta-analysis kind of thing? These are the two that were statistically significant on the pain scale.

DR. MEISNER: Sure. Can we put up the opioid meta-analysis, please? Yes, thank you.

So this is a forest plot, which shows the overall opioid use for all the trials, and it was all reduction in favor of SABER-bupivacaine treatment, and the overall difference in opioid use did not span the unity line.

DR. LITMAN: Dr. Goudra?

DR. GOUDRA: Basavana Goudra. What's the maximum recommended dose? Maybe you mentioned it.

I missed it.

DR. MEISNER: Of our drug?

DR. GOUDRA: Yes.

DR. MEISNER: The only recommended dose is 5 mL.

DR. GOUDRA: What would happen if you give more?

DR. MEISNER: We've actually done some studies where we did give more. We had several patients who got 7 and a half mL, and we had a fair number of patients who got 7 and a half mL plus another 75 milligrams of bupivacaine.

Slide up, please. I think I showed this slide once before. In some of our very early studies, there was a question of whether one might want to give both at the same time. None of the patients in this study showed any evidence of LAST.

That's what you wanted to know.

DR. GOUDRA: Did it measure the plasma concentration after rating doses?

DR. MEISNER: We did, yes.

DR. VERITY: As far as PK in terms of plasma

curves, with a 7 and a half mL, actually the Cmax really didn't exceed anything greater that we saw with 5 mL. But when you measured the area under the curve, it was dose proportional, linear kinetics, between 2 and a half, 5, and 7 and a half mLS.

DR. GOUDRA: Thank you.

DR. VERITY: Actually, while I have this slide up, if I can just make one more comment on it. One thing to note is 7 and a half mLS of SABER-bupivacaine is 990 milligrams of bupivacaine base. So in these studies, which we really saw no difference in AE reporting, either incidence or frequency, compared to other studies that had 5 mLS, although not a direct comparison because they weren't done at the same time, it's of note that we essentially gave over a gram of bupivacaine to these people, 990 of it released and well controlled by the same metrics, of which 50 mgs or 75 mgs was actually bupivacaine hydrochloride given on top at the time of end of surgery.

I believe Dr. Z had a question earlier, have

you ever done a trial where you've co-administered both be bupivacaine hydrochloride and SABER-bupivacaine. There's actually two trials listed here, and I'll walk you through it because it answers another question that you raised.

The first one, CLIN004-001, was a very early hernia trial during the development program, where we were looking at a different route of administration. This was a subcutaneous trailing injection as a paired injection on either side of the incision. So you take the 5 mL dose, divide it into 2 and a half and 2 and a half, and using that trailing injection technique that Dr. Meisner explained for the longer incisions, we applied it here.

This patient, or the people in CLIN004, that was how the drug was administered. As part of that study, 45 patients actually had an additional 50 milligrams delivered at the time or immediately after when SABER-bupivacaine was administered. The thought at the time -- because literally this was our first trial in hernia -- would be like similar

to Exparel, that perhaps the release rate from the depot was not fast enough to cover the first couple hours of pain once the patient's waked up. It turned out there was no difference in pain recovery curves using this subsequently forgotten about route of administration, whether or not we had the additional bupivacaine hydrochloride on or not.

The second study, which addresses another one of Dr. Z's questions, is that these patients actually had their hernia operation performed under local anesthesia, so they were not under general anesthesia. So here bupivacaine hydrochloride was given as the local anesthetic, ranging from 75 to 100 hundred mgs at the time prior to surgery. Surgery was performed, and then either 5 or 7 and a half mLs of Posimir or SABER-bupivacaine was administered at the close of surgery.

So we do have data that suggests from a AE perspective that you can administer a short-acting, local anesthetic along with our Posimir or SABER-bupivacaine formulation. But at this point in time, since this database is relatively small,

we would recommend not doing so.

DR. LITMAN: Thank you.

Jay, you had your name up.

DR. HORROW: Jay Horrow. No, it's asked and answered.

DR. LITMAN: Thanks. Dr. McAuliffe?

DR. McAULIFFE: I just want to follow on the idea of the 5 cc only recommended dose. Would that be the recommended dose if somebody was putting it in around a thoracoscopy, or a chest tube, or something like that, a very small incision, a very vascular area? And if that is the dose, would you also anticipate then the amount of bruising in that area to be the same amount of bruising that we would see in the larger incisions?

DR. VERITY: Two answers. We predominantly see bruising on the abdomen, and we have not studied the other surgical procedures that you've mentioned here. With regards to small incisions, you recall that in the lap port or the chole, are they called -- the small port surgeries that we've done, we've actually administered the 5 mL into a

very small incision, but equally dividing between the 2 or 3 ports.

So we think 2 points; 5 mL goes a long way as evidenced by the long laparotomy surgeries that we've done, but also it's safe to put into a small port, a relatively large volume into a small port. But in particular as to those types of surgeries that you've performed, I don't have any data on that.

DR. LITMAN: Dr. Zaafran?

DR. ZAAFRAN: Sherif Zaafran. Actually, that kind of prompted me to -- so in the longer incision, is there any reason why you can't dilute this into a larger volume but the same number of milligrams? For example, that 40-centimeter incision, is there a contraindication to dilute it up to 20 cc's, for example, with the same number of milligrams, but to inject that volume over a longer incision?

DR. VERITY: So SABER-bupivacaine is hydrophobic and does not mix with water, so you can't dilute it with saline or anything like that.

It would just be a blob at the bottom of the syringe, and you would not want to add additional SAIB and benzyl alcohol or other solvents in order to dilute it. So we recommend the 5-mL dose suitable for most incisional sizes that are seen across a variety of surgeries.

DR. FALTA: Could you aerosolize that?

DR. LITMAN: Sorry, Dr. Falta. Say your name before you speak to get into the record.

DR. FALTA: Edward Falta, general surgery. I was just curious if you could aerosolize the applicator.

DR. VERITY: Not the current formulation, but we have done other studies with other formulations where you actually can and use that as spray.

DR. LITMAN: I have a question. Have you ever looked at the correlation between your blood levels and your pain relief?

DR. VERITY: We have, and there's minimal correlation, so the PK/PD relationship really doesn't exist, as with bupivacaine hydrochloride.

DR. LITMAN: Yes. It just makes me wonder. I'm still having a hard time envisioning pulling a teaspoon through a large incision and how that could be effective. It just got me thinking maybe it had something to do with blood levels.

DR. VERITY: Yes. To follow up on that, all the drug that's measured in the plasma is wasted drug. Where you need the drug is at the site of action and that's the incision. So we use PK as measurements for safety and surrogate measurements for performance of the depot. But the reality is where you need the drug is actually where you put it, and that's in the incision.

DR. LITMAN: Any other clarifying questions for the sponsor?

DR. VERITY: I could actually clarify one or two more questions from this morning.

DR. LITMAN: Sure.

DR. VERITY: The gentleman on the end, sorry, asked if it was standard error or standard deviation, and we believe it to be standard error, but knowing that the N is only 5, the standard

deviation would be only about twice what you see.

DR. HORROW: This is Jay Horrow. Thank you for that clarification.

DR. VERITY: One other clarifying point I may offer up is that we do have in our bullpen an expert on pain, who I think might be able to give to the committee, as well as ourselves, a little education on the MCID and/or the clinical relevance of the product.

DR. LITMAN: I'm not going to allow that just because it's not an answer to a clarifying question, but thank you.

DR. VERITY: Understood.

DR. LITMAN: Dr. Roca, you're up. Dr. Roca will now provide us with the charge to the committee.

Charge to the Committee – Rigoberto Roca

DR. ROCA: Thank you. I do appreciate that you've heard quite a bit of information, different studies, different designs, different purposes, and different anatomical sites. I think the comment that was just made a few minutes ago is quite

helpful as well in the context that the PK/PD relationship doesn't seem to exist; that the blood plasma levels are primarily used for safety. Therefore, efficacy is really more of a local thing, therefore you think about the fact that the efficacy from one particular site may or may not be extrapolatable to another site. You also heard information regarding some of the safety findings, et cetera.

With the first discussion point -- and it's actually a tough question to ask you all, but basically with all the information that you've heard, whether you feel that the applicant has provided sufficient information to support the proposed indication as was read this morning.

As you discuss that, that will lead you to the second point, which is whether there are any issues left within this complete response resubmission that still warrant additional studies and to comment on whether you think these could be done before or after approval.

When you put all that together, we come to

the third discussion point, which is whether the efficacy, safety, and the overall risk-benefit profile -- or the other way you can look at it is whether the efficacy and safety information you've seen results in a favorable risk-benefit profile that will support approval of the application.

As we've done before, we end up with a voting question where we're asking you whether you recommend approval of the product as noted there for the proposed indication, and as you've done before, if you voted yes, your rationale and whether you feel that any post-approval study should be required. Similarly if you voted no, to discuss your rationale, and particularly at that point whether additional data are needed for approval.

I know it is a big task, and I appreciate, and I'm looking forward to the discussion. Thank you.

Questions to the Committee and Discussion

DR. LITMAN: Thank you, Dr. Roca.

We will now proceed with the questions of

the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Can I please have discussion question 1? Please discuss whether the applicant has provided sufficient information to support the proposed indication. As always, put your name tags up, and we'll keep a running tally and try to get you one by one.

Dr. Zaafran?

DR. ZAAFRAN: Thanks. Sherif Zaafran. The one bit of information that most supports the answer to this question is the time to the use of the first opioid. In those two studies, one with the inguinal hernia and the other one with the subacromial decompression, there is a marked difference.

The only thing that I hesitate with is not knowing what was given during the general anesthetic. So if there was a suggestion that I

would have that would clarify that, it would be that you can't do it with a subacromial decompression, but at least with the inguinal hernia -- or with those, to actually control it using a neuraxial technique where you're not getting any type of narcotic whatsoever and to look at the comparisons of the first-dose narcotic. Then you're really kind of taking away all the other confounding bias that might be there.

It would also answer the other question about all the other adverse events, the nausea, the vomiting, the somnolence, all the other stuff, which could be confounded by all the different types of general anesthetic medications that you're giving.

You're taking all of that away and you're normalizing it to just numbing half the body and figuring out is that one medication causing or allowing or affecting a longer period of time for the first dose of opioid to be given. That would give me a much stronger feeling that this medication is working as indicated.

DR. LITMAN: Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. I agree. I do think that the applicant has provided sufficient information. I'm going to go a little further than that and ask the FDA a question about what would be permissible postmarketing in terms of study. I'm imagining that comparative studies would not be permissible postmarketing, enrichment studies to focus on some of the safety concerns. What is permissible?

DR. ROCA: Definitely if there are any questions regarding a safety issue that you would like to have cleared up, identified, you can certainly do that. I'm trying to figure out whether an efficacy study, per se, would fall into that category. I know that we're thinking that sometimes that would be beneficial, particularly if you're trying to assess efficacy also in view of safety concerns.

So you're trying to weigh both so that you end up actually requesting not a safety study, per se, as you would imagine a safety study would be

designed and powered, et cetera, looking just for safety findings, but an efficacy study that would also be looking at safety but putting into context the efficacy.

So to a certain extent, the kind of studies that would be allowed or permitted in the post-approval stage would be depending on what questions the committee thinks would be useful to try to address.

DR. HIGGINS: Thank you.

DR. LITMAN: Dr. Horrow?

DR. HORROW: Jay Horrow. The proposed indication does not include any time scale on it. Given the likelihood that the clinical trials section of the label will show data out to 72 hours, I believe that consideration of the duration of action of the product is under discussion. From a scientific perspective, I'm struggling with visual issues of data transparency both on the part of the sponsor and the FDA.

The sponsor in slides 39, 40, 45 and 46 presents data with standard errors of the mean

rather than standard deviations. Most critical journals insist that data be presented graphically with standard deviations rather than standard errors of the mean. They also provide lines that connect the dots even though there are no data for those connecting lines. All we have are data at the time periods.

The agency presents only the lines, not even the dots, and no errors whatsoever, and that makes it very difficult for panel members to understand and to evaluate the data; although the FDA, I believe, correctly identifies and calls into question any effect that might occur beyond 12 hours.

Visually to the person looking at these graphs -- and by the way, the FDA slides in question are 19, 23, 32, and 33. To the person viewing these graphs, we focus on the area under the curve and any differences between those areas, although it's unclear whether this is a correct outcome variable to assess whether or not the test substance actually is a long-acting anesthetic. It

gives, in my impression, an incorrect visual impression of what we should be getting out of the data.

An unbiased evaluation of the data at time points greater than 12 hours, showing absolute mean differences with 95 percent confidence intervals and with or without nominal p-values, would be appropriate. As we know, even though those curves look like they are separate beyond 12 hours, we know from the FDA, who has tested those points, that in fact there is no difference, but visually it looks like that. The sponsor repeatedly said visually you can see a difference, but we know that we can be tricked visually. We need to see the data and the nominal p-values.

Now, the meta-analysis itself has separate issues relating to that. I saw no measures in the meta-analysis of heterogeneity, no chi-squares, for any of the curves that were presented. There's dubious rigor for the meta-analyses, and I'll be happy to discuss the meta-analyses separately when we consider discussion point number 3. But I'm

just struggling as somebody looking at the data to come away with a proper interpretation. Thank you.

DR. LITMAN: Thank you. Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff. With respect to this question, the sufficient information, I would agree with everything Dr. Zaafran said, first of all, which made me not have anything to say. But then with respect to what we heard just a few minutes ago, for the first time this technique for long incisions about withdrawing a catheter and squirting as you withdraw, I have no image of what I would use or where I would go in the operating room to get a line tubing or what kind of catheter I would use; whether it would look like a surgeon's drain that I would infuse this through as I was pulling it out. So I'd have to say that I was not provided sufficient information about this, quote/unquote, "long incision withdrawal technique." Thank you.

DR. LITMAN: Dr. Goudra?

DR. GOUDRA: Basavana Goudra. In spite of all of the limitations so elegantly described by

Dr. Horrow, especially in connection with the meta-analysis, having published all 10 meta-analyses myself, I don't even think that this will fit the definition of meta-analysis. But in spite of everything, I think the applicant has demonstrated its benefits, at least when it's compared with the placebo. That's the FDA requirement. I think they've done the job that's required.

DR. LITMAN: Dr. McAuliffe?

DR. McAULIFFE: I'm looking at the question to support the proposed indication, which I am assuming is postoperative incision. The orthopedic case was a closed orthopedic case and not an open shoulder, and the open shoulders, as we know, are the most painful orthopedic cases, in the shoulder region anyway. So I don't know that it does give us enough confidence that they've provided sufficient information, for at least every proposed indication. Thank you.

DR. LITMAN: Dr. Cullen?

DR. CULLEN: I just want to make a comment

on what was just spoken about. I agree with Dr. Zacharoff. As a surgeon, I can't get my head around how you would do that, and I'm the guy doing that. I don't know why it's just placed on the wound and close the skin over, so that catheter thing doesn't make much sense.

What I would like to have seen, which was just touched on, was the shoulder operations. I'm not an orthopedic surgeon, but those patients have a level of pain preoperatively, and it would have been nice in the shoulder segment of their studies to see what their pain scores were prior to the operation, because I think that might have an effect.

Finally, I keep on looking at the slides, I think it's 39 and those other ones. The initial effect of this medication is in the first 12 to 18 hours, it looks like. After that, I just can't -- to me, it doesn't suggest that it's working for 72 hours.

DR. LITMAN: Dr. Shoben? Sorry. You're too close.

DR. SHOBEN: Sorry. Abby Shoben. I just wanted to say that I think I really agree with the FDA's characterization that it's a modest, at best, and inconsistent effect. If you look at -- you're not seeing sort of the same -- what you would like to see ideally is a consistent, similar effect across a variety of surgical sites with this sort of nice, what they were powered for, 1-ish point difference supported by the opioid-use data being in favor of the new drug, and you just don't see that. There are just so many trials where you see smaller effects and very modest benefits, and that's really problematic to me in terms of supporting this indication.

DR. LITMAN: To sum up, I think I heard that we needed more information in general about the anesthetic regimens to properly put the comparisons into proper context. I heard that some people felt that there were very significant limitations of the data interpretation, based on varying visual analyses that were tough to interpret.

We as the ADCOM, I feel like we're sort of

caught in this weird place here today, where we came in looking at the FDA briefing booklet, and the sponsor presented an awful lot of additional data. Almost both sides had a lot of cumulative data, and it was really difficult to understand what all that cumulative data meant. It seemed that at times each side kind of used the cumulative data to support their interpretations.

I do agree with Dr. Horrow about the meta-analysis, and I'd go one step further that -- I can tell you as a journal editor and frequent reviewer, meta-analyses are one of the most common articles that we get to review, and the heterogeneity is so frustrating, and I don't think they're appropriate for FDA approval.

I also heard limitations on interpretation of technical methodologies such as the instillation method, but on the other hand, I also heard some opinions that thought that they did provide sufficient information to support this specific proposed indication.

Did I capture everything?

(No audible response.)

DR. LITMAN: Question 2, please. Discuss whether there are issues with this complete response resubmission that warrant additional studies and, if so, should these studies be conducted before or after approval? Dr. Zeltzer?

DR. ZELTZER: Lonnie Zeltzer. I think it was in the requested -- I can't remember whether you had discussed it here or whether it was in the materials of what was requested. But while there is no IV indication, as was mentioned, in the OR you can see lots of risks that are unintended, like something being given IV when it shouldn't or a very bloody area and something happens. We don't have any preclinical data on risks if this were in this amount and width, its adjuvant, if it's given IV, and that's a concern in terms of potential unintended consequences and risks.

DR. CHOI: Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff. With respect to this discussion point, as we already discussed with respect to question 1, additional

studies, possibly after approval, that control more for the use of intraoperative analgesic administration that allow for a greater level of comfort with respect to regional anesthetic techniques, et cetera, et cetera, I think could be very valuable.

I did hear loud and clear the idea about really not having a good sense about what the demographics of these patient populations were, and it's really hard for me to say when I think of inguinal hernia patients or certain other types of common surgical cases, that I have an image in my mind of some age groups, but I think that that could be beneficial as well.

Given that this is a fixed-dose medication based on volume, it's entirely possible that there could be some patient populations where what we would consider to be a high dose could end up being a super high dose. So again, I think that that could be conducted after approval. Thank you.

DR. LITMAN: Dr. Goudra?

DR. GOUDRA: Basavana Goudra. The only

post-approval study I would certainly recommend is in animals if given intravenously, whatever the dose, to see whether Intralipid is effective to treat it, because there will really be a day when some of us are going to inject intravenous accidentally, and there's no debate about it. All kinds of stuff has been injected, including by myself. Thank you.

DR. LITMAN: Dr. McAuliffe, did you have a question?

DR. McAULIFFE: I do. I think that we're making some assumptions that the postoperative drowsiness and somnolence is related perhaps to the anesthetic or the opioids that are given. We don't know that. And it could be related to the benzyl alcohol. So I think that a study needs to be done to determine what's causing this. What scale are we using to measure somnolence? It was sort of dismissed a little bit that it was a false positive; that it was solicited versus self-reported.

How does a patient who's in the recovery

room tell you I'm drowsy? That's a self-report. So I think we need to kind of have a scale and find out exactly what it is, and then figure out what's causing it.

DR. LITMAN: Dr. McCann?

DR. McCANN: Mary Ellen McCann. I don't know whether testing should be done before or after, but I have issues, like everybody else, with the vehicle of administration. I think if this were a single-use spray, that it would be hard to misuse it. I think you put a syringe in the hands of doctors or nurses, it's just going to get used incorrectly at some point, and it could have tragic results when that was done. If it were a spray and it worked, I think it would be much, much safer.

DR. LITMAN: What about prepackaging it with a 5-cc syringe only attached to some kind of an applicator that Dr. Zacharoff or Dr. Cullen was talking about, of some sort?

DR. McCANN: I think that would be a step in the right direction.

DR. LITMAN: Dr. Zaafran?

DR. ZAAFRAN: Sheriv Zaafran. I just want us to also be careful that we're holding folks to the same standard as what we do in the operating room right now. We routinely draw up local anesthetics in syringes and inject it into tissue -- or surgeons do of course -- intraoperatively, routinely. Is there a risk that it could be injected intravascularly? Yeah. When you're locally infiltrating into tissue, that's probably a little bit higher risk as opposed to just kind of dropping it onto the wound.

Now, I think there may be some value in a bloody site where there could potentially be some absorption there and what the risk of that might be. But if you're talking about an incision that you're closing -- I don't really know of many surgeons who'd be closing an incision that's very bloody. That's one of the things that you guys worry about and watch out for all the time. So I'm not sure I'd worry about that as much because it's not very different from what we do already today on a routine basis.

DR. LITMAN: Dr. Falta?

DR. FALTA: Edward Falta, general surgery. I think one of the things that confounds the postoperative symptoms is that they're mixing visceral surgery with somatic surgery and testing a somatic analgesic. I thought maybe postmarketing or post-approval, studies would be kind of more specific for a somatic surgery, like a hemorrhoidectomy, or umbilical hernia, or like a burn debridement, something that doesn't involve visceral surgery.

DR. LITMAN: Mary Ellen, do you still --

DR. McCANN: Well, to your point, we don't ordinarily put 660 milligrams of bupivacaine in a syringe. I think that's where the danger comes in, even more so.

DR. LITMAN: Any other comments about question 2?

(No response.)

DR. LITMAN: In sum, I think I heard a couple of different themes here. One was some concern about how to put the comparisons and the

results in context; one based on demographics and the other one, which is I think an important point, that the studies were mixed. Not all pain is the same and not all pain responds to local anesthetics in the same way.

The other theme I heard here was that there would be some need for some further studies to better define the risk. I definitely agree with Dr. Goudra that even though there is no theoretical reason why the treatment of local anesthetic toxicity wouldn't be appropriate, I can't imagine you just can't take two dogs and make sure you can rescue them; just not labs.

(Laughter.)

DR. LITMAN: What's causing the somnolence? In further studies on the instillation, one of the things I think some of us agree on is that in all the studies that were done, there must have been so many variety of ways that the drug was put into the wound, whether it's the 40 centimeters dragging method or the laparoscopic method which, again, if you're doing a cholecystectomy, how many holes do

you have guys, 3, usually 4? How do you put a teaspoon into four different holes? I know. I see these every day, and I can't even imagine. So I think those things need to be further defined.

Did I capture everybody's --

(No response.)

DR. LITMAN: -- okay, question 3, please. Discuss whether the efficacy, safety, and overall risk-benefit profile of Posimir support the approval of this application. Here now we're talking about just overall risk-benefit, your impressions.

Dr. McCann? In doubt?

DR. McCANN: No, I forgot to put it down, but I just did do the division, and maybe I did it wrong. But if you were comparing it with 0.25 percent bupivacaine, it's equivalent to 264 mLs. I mean, that's a lot.

DR. LITMAN: Dr. Cullen?

DR. CULLEN: Joe Cullen, surgery. One thing that the FDA presented, we looked at headache and nausea and vomiting. If you look at those

percentages, I not only thought they were not statistically significant between the different medications, but I didn't think they were clinically significant either.

Having said that, I still think that first 12 to 24 hours that you see the difference in the drug, a lot of that could be due to the anesthetic that was given and what was given during the anesthetic, especially in the first 12 hours. So I think it's a safe medication. I don't think these differences we see in the patient groups are significant both statistically and clinically.

DR. LITMAN: Dr. Horrow?

DR. HORROW: Jay Horrow. I'm still struggling to convince myself on the efficacy part, and of course if we're not convinced of efficacy, there's no reason to even discuss safety. Understandably, this product was designed to be long-acting, so the efficacy studies contained a primary outcome variable that should show that effect, namely the area under the curve from 1 to 72 hours, I believe, with the hope that 72 hours

would be the duration of effect.

However, when we look at the individual time point data, we scratch our heads about whether we're seeing an effect much beyond 12 hours. And I, for one, question seriously drawing straight lines in between 2 data points and believing that there's a linear effect there.

As we know, there are certain thresholds for drug concentrations for effect, and if that threshold is breached, then the effect wears off. So even if the amount of drug is going down linearly, that doesn't mean the effect of that drug is linear; so I struggle with that.

That then leads us to the sponsor's argument of looking at not necessarily the pain scores that we see in those data points, but the time to first opioid use as rescue as an outcome variable, which it wasn't. It was a secondary variable, and that then raises the question of whether the data could be -- whether another study could be done with that as the outcome, the primary outcome variable submitted as evidence of efficacy.

Suffice to say, looking at the Kaplan-Meier curves, there are very few events for opioid requests beyond 16 hours, and I'm referring to slide 48 of the sponsor's presentation. And I believe it's those Kaplan-Meier curves that are the correct ones to present and not the forest plots for meta-analyses that we were shown.

That makes me think that, in fact, what's happened here is it doesn't matter what you got in terms of pain relief, after a certain period of time, most people don't feel pain anyway, or at least not enough to require an opioid. So that raises the question as to whether you even need, in the models studied, a long-acting local anesthetic.

So I'm struggling to understand the efficacy here. If I can't get my arms around the efficacy, then I certainly can't evaluate benefit-risk when it comes to any of the safety issues. Thank you.

DR. LITMAN: Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff. With respect to this question, probably my biggest concern with respect to the overall risk-benefit

profile was the post-procedural contusion issue. If Dr. Cullen gave this to a patient in the operating room and then is being covered by me, and I'm seeing the patient 2 days later, and I see this, if I haven't received the proper amount of education, I might think there's a hematoma developing.

I haven't seen a photograph of what this post-procedural contusion was, but I did hear descriptions about size and the palm of my hand. I would imagine that with a relatively small incision, but yet post-procedural contusion that might persist for up to 30 days, that I might be concerned, and that concerns me from the safety and risk perspective.

With respect to the other issues, I think in a real world, what we've already heard said, and I would just reinforce, is that I would be gauging its efficacy based on the amount of opioid that somebody needed to be administered before, what Dr. Gan spoke about very much earlier today, and has recovery after surgery. That is something that

is intended to get patients out the door relatively quickly with relatively few complaints.

I think that whether we're talking about the first 24 hours or the 24-to-72 hour period, Dr. Horrow, you might be absolutely right, that it might not make that much of a difference. But what was different was that the patient didn't require a lot of narcotic. There wasn't some amount of period of time that they needed to be observed after they got a dose of narcotic, and they were able to get out the door and be on this enhanced recovery track.

So if I take it all into perspective and don't necessarily worry as much about what the potential for intravenous injection might be, even though I do agree with that as a post-approval study -- this is not a case where an anesthesiologist is going to pick up a syringe with a clear solution in it and accidentally inject it intravenously. This is a situation where a surgeon who scrubbed is going to be administered this drug that is likely delivered to them by the scrub

technician, who will have received it from the scrub circulating nurse in the operating room, and there should be enough checks and balances in place to make sure that the right medication is getting delivered without a needle into the right location.

If this was an anesthesiologist injected drug, I think the risk of intravenous injection might actually be higher, to be honest with you, and we all know how labeling syringes and abbreviating terms and things like that could happen. So post-procedural contusion is the thing that concerns me the most here, and the educational challenges from a safety perspective is what concerns me the most. Thank you.

DR. LITMAN: Dr. Zaafran?

DR. ZAAFRAN: Sherif Zaafran. I don't know if there's enough to suggest that it's equally efficacious in the long term or as a long-acting, but there does seem to be enough evidence to show that it is better than the current or similar local anesthetics in the short term. So when I think of C-sections, for example, where you could apply it

over the wound, or when you look at, again, inguinal hernias or others, where these are surgical center patients, just looking at the data, it looks like you could get these patients out of the surgery center without having to give them any opioids, that to me is fairly meaningful.

So from the standpoint of efficacy -- and I heard from the FDA earlier that they would more than likely in the labeling put down a specific time period as opposed to, say, a long-acting, short-acting, whatever, which wouldn't really mean much. But it is fairly meaningful that the number of hours before you give an opioid is significantly longer, at least looking at that one inguinal hernia study, and even the other one. Even though you're not comparing it directly to bupivacaine, I would, if it potentially gets approved in the post-period, re-look at general anesthetics versus neuraxial anesthetics and see if those adverse events would actually be significantly less.

I think the way it is right now, it's probably just as much. I think if you took a

general anesthetic patient, in general, without anything at all, you probably may see those exact same numbers. The question is that if you didn't have to administer general anesthetic, would it be any higher than somebody who didn't receive anything at all except for 12.75 milligrams of bupivacaine intrathecally.

So from that standpoint, I think the safety and the overall risk-benefit profile is not any higher. There's not any additional risk except for the contusion standpoint. But efficacious, I think it is in the short term, and it is something that seems to be better than at least bupivacaine by itself.

DR. LITMAN: Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. I feel comfortable with the risk-benefit profile, and there are some modest safety concerns, the contusions. Some of the CNS, I don't mean to make light of those, they're very significant, but do feel like that could be surveilled postmarketing. I like the fact that it's an opioid-sparing

medication, and we don't come across many of those. And I really appreciate the fact that the sponsor took the time to enroll folks who are above the general age cutoff and up to age 87, which makes me feel more comfortable for the older adult population as well.

DR. LITMAN: Dr. McAuliffe?

DR. McAULIFFE: I too am worried a little bit about the postoperative bruising, and 90 percent of the patients had a postoperative bruising that could be as big as a man's hand, and I think that's fairly significant. I think that does interfere with the matrix of the tissue. It predisposes potentially to postoperative infection. And I'm worried about certain subgroups of patients, patients with cancer, or patients who are prone to infection with diabetes. So we don't really know that that's more of a problem than what we're just kind of seeing here.

DR. LITMAN: Dr. Horrow? Did you -- no. Dr. Shoben?

DR. SHOBEN: Abby Shoben. I want to echo

Dr. Horrow's comments in terms of -- my concern here is really with the efficacy. I don't really see the level of efficacy that some of you seem to be seeing. If you look at PERSIST, which was the trial that was done as part of the complete response rate, Part 1, where they were looking at saline placebo, you see -- this is in a lot of places, but it's on FDA slide 30. You have this mean difference of 0.8 compared to the placebo control, and that didn't reach statistical significance. Then the comparison with bupivacaine, where it was powered to look for a difference with just plain bupivacaine, you see a difference at 0.3, which is clearly not statistically or clinically meaningful.

So really, I'm struggling with the efficacy part here. Because I'm struggling so much with the efficacy, what would otherwise be minor safety concerns about the bruising and some of the minor signals of bleeding, it just becomes a little bit more magnified because there's so little efficacy.

DR. LITMAN: Before I sum up, I'll add my

own opinion. I think that taking into consideration the risk, I'm not that concerned with the contusions and some of the minor things. My most important concern is theoretical, as Dr. McCann alluded to before, putting 660 milligrams of bupivacaine with the potential for intravascular injection. The problem is that it hasn't happened, and there's no way that we here today can define what that risk is.

As I mentioned before, I feel pretty confident in saying that it will happen eventually, but does that mean that that should tip the balance? Everyone's going to have to have their own opinion here as to whether or not that's significant enough to compensate for the benefits. The benefits, it was really hard to tell what the benefits were here today. We've heard so much different data from both sides, much of which was cumulative and in many different types of patient populations and anesthetic conditions.

If you think about what we're doing now, which is bupivacaine in most of my cases -- I'll

confirm with the surgeons who use bupivacaine with epi or plain -- we're getting about 6 to 10 hours maybe. That's probably exaggerating; probably 4 to 8 is my best guess. Anything beyond 8 hours -- I don't care about 72; anything beyond 8 would be a big improvement over what's on the market right now, at least for a local, and, if we could, avoid opioids for a few days or even NSAIDs.

So I think the risk-benefit ratio, honestly, it's really hard to tell. I don't have a really good grasp. The only thing I will say is this drug, the original NDA was 2006? You would think we'd know by now. That's the thing that keeps nagging at me. So those are my personal views here.

So to sum up, I heard a mixed opinion. I heard some people are very concerned about the contusions. I heard a couple of different things about the benefits. Some people were satisfied with the benefits, and they thought that there was a favorable benefit-to-risk ratio, while other people, like myself, Dr. Horrow, could not evaluate

it properly in the context of the data that was presented. So it's a really difficult choice. It's a really difficult equation to try and come up with on one side or the other, and I think that's what we're hearing, is a gestalt of what I'm getting.

Did I leave anything out? Anybody else?

(No response.)

DR. LITMAN: So where's my script? Here we go.

So we never took a break. Nope? Is everybody okay without a break? Does anybody need a break? Can we take 5 minutes for people to run to the bathroom and back before we go with the voting? Is that alright? Thank you.

How about this? We'll take 9 minutes. It's 2:21. Please come back at 2:30.

(Whereupon, at 2:21 p.m., a recess was taken.)

DR. LITMAN: It's 2:30. It looks like everybody's back.

We will be using an electronic voting system

for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or if you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the screen. The DFO, Moon, will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed.

Question 4, which is the vote, do you recommend approval of Posimir bupivacaine extended-release solution, 660 milligrams per 5 mL or 132 milligrams per mL, for the proposed indication of single-dose instillation into the

surgical site to produce postsurgical analgesia?

Are there any questions about that question; any concerns or --

(No response.)

DR. LITMAN: -- okay. Just to clarify because I know this will come up. It says "extended release," and we don't know what that means, essentially.

A, If you voted yes, please discuss the rationale for your vote and specify whether any post-approval studies should be required. If you voted no, please discuss the rationale for your vote and what additional data are needed for approval.

Are there any clarifying questions before the vote?

(No response.)

DR. LITMAN: Okay. Please press the button on your microphone that corresponds to your vote. You have approximately 20 seconds to vote. Press the button firmly. After you have made your selection, the light may continue to flash. If you

are unsure of your vote or if you wish to change your vote, please press the corresponding button again before the vote is closed. When everyone has voted, we will be signaled that the vote is complete, and we will reveal the votes.

(Voting.)

DR. LITMAN: The vote is complete.

DR. CHOI: We have 6 yes, 6 no, zero abstentions.

DR. LITMAN: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record.

Moon, is it possible to put up the A and the B choices again so the panelists can see what the FDA is interested in? No, we can't. Okay. So hopefully everybody remembered. If you stated yes, did you want further studies? Was that what it was?

Dr. Roca, would you mind reading that again just so we're clear? Oh, actually I have it. I

apologize. I got it right here.

If you voted yes, please discuss the rationale for your vote and specify whether any post-approval studies should be required. If you voted no, discuss the rationale for your vote and what additional data you would want for approval. So we'll start with Dr. McCann.

DR. McCANN: I voted no. I was convinced by what Dr. Shoben and Dr. Horrow said. The safety issues were definitely there for me as well, but mostly I was concerned that they really didn't demonstrate efficacy. Further studies that demonstrate efficacy would be useful in the future for me to vote yes.

DR. ZACHAROFF: Hi. Kevin Zacharoff. I voted yes for pretty much what we've discussed with the last four discussion points. My yes has the asterisk about doing post-approval studies regarding intravenous administration in animal testing to see if it can be reversed by Intralipid. My yes is also qualified by some type of packaging that would include a delivery device that would

enable somebody to administer this withdrawal administration without leaving it up to everybody's own ingenuity. Thank you.

DR. McAULIFFE: Maura McAuliffe. I voted no based both on limited time demonstration of efficacy in the more invasive surgeries, especially orthopedic surgeries, and also reliance on post hoc analysis for explaining potential safety risks with respect to wounds and to neurological events that were measured. What could be done? Prospective, well-designed, well-controlled studies to look at those factors and demonstrate that they aren't safety risks.

DR. ZELTZER: Hi. Lonnie Zeltzer. I voted no. Mostly, I wasn't convinced of efficacy beyond 12 hours from the data presented. I still think that it would behoove the company to have an administration package for consistency of administration before it gets approved rather than hoping it will all work out afterwards. From a safety standpoint, I'd like to know what happens if IV, this amount comes into the intravenous system

and can it be reversible.

DR. GOUDRA: Basavana Goudra. I voted yes. The reason being it's not a magic bullet, we all know that. Such a thing probably doesn't exist. It's certainly better than placebo and probably better than standard bupivacaine, at least in some situations, some procedures. The contusion, or whatever, the swelling, I think it's minor. Accidental IV is my biggest concern, and I should know whether I'm going to put this patient on a cardiopulmonary bypass machine or I'm going to give it a shot with Intralipid. So that certainly needs to be done. But other than that, I think this drug should be ready to go.

DR. LITMAN: This is Ron Litman, and I voted no. This was a tough decision. I felt conflicted and confused from the beginning of the meeting because the data that was presented by the sponsor was not reflective of what I had prepared for this meeting, so I really didn't know how to adequately assess their benefit data. I can't assess their risk data because the most important risk for me is

the accidental injection, and I don't know how to assess that. It's just a feeling. So when it all came down to it, I would love for this drug to work.

As I mentioned before, anything that extends post-op numbness, anesthesia beyond 6 or 7 hours, would be a huge improvement; not just incremental, it would be huge. Overall, I just felt that the risks outweighed the benefits based on what I heard today, but that may not be the case. If the FDA ends up approving this, I would ask you to be very careful in the kinds of clinical studies you portray on the label because that will determine what the marketing says.

So I don't think the marketing will say long-lasting or extended release. It's going to say effective up to such and such hours, and obviously that's constrained by what's on the label, and that's what you guys determine.

DR. SHOBEN: Abby Shoben. I voted no. I think I've expressed my efficacy concerns pretty earlier. It was a tough decision because I do

think if you made me bet, I would say it is probably very slightly better than placebo, but the concern is that very slightly better than placebo coupled with some potentially relatively minor safety concerns makes that benefit-to-risk calculation really challenging.

I do think that the response the sponsor had looking at the PERSIST data and looking at the safety relative to bupivacaine, and doing the stratified analysis looking at solicited versus spontaneous reporting was really helpful in terms of really clarifying the safety issues. But in the end, with such a minor efficacy signal, even remaining minor safety concerns was what pushed me toward a no vote.

DR. HIGGINS: Jennifer Higgins. I voted yes for many of the reasons already stated. I think it's a promising opioid-sparing product, and I like the fact that it provides a new option for people, such as the woman who spoke in the public hearing session with an allergy to certain medications.

With respect to postmarketing exploration, I

would say continued safety monitoring, obviously, and then mitigation of some confounding variables such as surgical procedures, and then the anesthetics that have been discussed today, too.

MR. O'BRIEN: Joe O'Brien, and I would say it's probably the most difficult decision that I made voting yes, and I voted it because I was conflicted, I was confused, I was concerned. I think that when I read through all the materials and then listened to it, I had a sense that it was fake it until you make it. I thought that the data was inconsistent, and there are some unknowns that I don't understand that don't seem to make sense with the rationale that I heard and that I saw.

As a patient who's had subtotal colectomies and 6 spine surgeries, I am very concerned for adverse events like for vomiting and nausea. While they may be short-term, they are very important to the patient that's there, and I just don't understand what I'm seeing, and it still doesn't make sense to me. In the process, it's explained with data -- I don't want to say manipulation, but

data movement -- in favor of something, and I just don't see the efficacy. I don't think it's strong that's there.

So despite all those concerns, at the end of the day, we do have a need for opioid-sparing medications. On top of the fact that this is a medication that's going to be driven by clinicians, anesthesiologists, and surgeons in the operating room, I let that be a level of safety for me to say, okay, let them take it there, but it is the most conflicting vote I've ever made.

DR. ZAAFRAN: Sherif Zaafran. I voted yes. One of the things I would say about the postoperative period is I think pain scores are relatively useless, and I worry that we're spending so much time focusing on that from a standpoint of efficacy. When you look at the decision by the patient to ask for their first dose of opioid medication, clearly being different with this medication compared to others, that to me is a stronger point of efficacy that I would look at in the postoperative period.

There's a vast difference. A point score of 1 or 2, I've seen people who have a score of 2 and want medication and people that have a score of 8 who don't want anything. So what does that mean? If you're not needing opioid medications and you're not asking for it, to me that's more meaningful because at the end of the day, what are we trying to do here? We're trying to minimize the use of opioids in the postoperative period, and hopefully that translates into less opioids in the longer term afterwards. That to me is more meaningful.

From the side effect standpoint, again, I'm not sure I see much of a difference from a general anesthetic with nothing versus with the medication, so it would be helpful afterwards to see that bias removed, whether by doing neuraxial blocks and using the medication with that; that would give a much clear indication.

The one caveat, I think we should have the intravascular studies on non-Labrador dogs, but that would also be helpful just to give a clearer picture from that standpoint.

DR. CULLEN: Joe Cullen. I agree with everybody that questioned the efficacy, including the FDA. That's why I voted no. I do think it's safe, however, the recent discussion regarding bruising, the data on that was very vague, and bruising is kind of a vague thing, so I think that that data needs to be teased out. I do think it's safe, however, I do have some concerns about the bruising issue.

DR. FALTA: Edward Falta. I voted yes. I felt that the first 24 hours was a great utility for an analgesic, and I agree with Dr. Zaafran with not requesting opioids in the first 24 hours is a very strong indicator of efficacy. I also think that you need a more consistent delivery vehicle than the catheter. I think a spray would probably be more consistent and safer. I also think that we need a postmarketing study comparing the standard practice with bupivacaine and epinephrine injection versus the application of this product.

DR. LITMAN: Thank you.

Dr. Horrow, even though you weren't voting,

do you have any last minute comments or editorializations for us, for the FDA?

DR. HORROW: Jay Horrow. I would say that despite the completely split 50/50 vote, thanks to the talents of our chairman, who conducted an excellent meeting, sufficient information has come from the participants of the panel, the sponsor, and the FDA to provide valuable information to the FDA to see a way forward that this drug might achieve approval someday. Thank you.

DR. LITMAN: Thank you.

Dr. Roca, any final comments before we adjourn, now that this is all clear?

DR. ROCA: I think I mentioned, when I gave the charge to committee, that the question was simple and straightforward, but the response obviously is not. I certainly appreciate all the discussion. It's obvious that you guys really thought about it, and some of you, as you mentioned, have really wrestled with it. I certainly understand that, and I do appreciate your time and your effort, and I wish everybody a safe

trip home.

Adjournment

DR. LITMAN: Thank you. We kindly ask that all attendings dispose of any trash or recycling in the proper receptacles in the hallway and not leave any waste items on the floor or tables.

Panel members, please remember to take all your personal belongings with you as the room is cleared at the end of the meeting day. Please leave your name badge on the table so that may be recycled. All other meeting materials left on the table will be disposed of. We will now adjourn the meeting. Thank you.

(Whereupon, at 2:46 p.m., the meeting was adjourned.)