FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANESTHETIC AND ANALGESIC DRUGS PRODUCTS ADVISORY COMMITTEE (AADPAC)

Thursday, October 11, 2018

7:59 a.m. to 3:54 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)

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Office of Executive Programs, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(7:59 a.m.)

Call to Order

Introduction of Committee

DR. ZACHAROFF: Good morning. My name is Kevin Zacharoff. I am the acting chairperson of the Anesthetic and Analgesic Drug Products Committee, and I will be chairing this meeting. I will now call the meeting of the Anesthetic and Analgesic Drug Products Committee to order.

I'd first like to remind everybody to please silence your cell phones -- something I just did because it would have been very embarrassing if I didn't -- and any other devices if you've not already done so. I would also like to identify the FDA press contact, Michael Felberbaum. If you're present, please stand. It looks like he's in the back there waving his hand. Thank you.

As we call this meeting to order, we'll start by going around the table and introducing ourselves. Maybe we can start here.

DR. THAN HAI: Good morning. I'm Mary Than

Hai. I'm the acting director of the Office of Drug Evaluation II, CDER.

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

DR. MAYNARD: Good morning. Janet Maynard, clinical team leader in the same division.

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

DR. SOLGA: Steve Solga, gastroenterologist and hepatologist at the University of Pennsylvania.

MS. SHAW PHILLIPS: Marjorie Shaw Phillips, clinical research pharmacist and pharmacy manager, AU Medical Center at Augusta University, and also without salary, clinical professor of pharmacy at University of Georgia College of Pharmacy.

DR. FISCHER: Mike Fischer. I'm an internist and a pharmacoepidemiology researcher at Brigham Women's Hospital and Harvard Medical School in Boston.

DR. GOUDRA: Sorry. Perfect timing. Dr. Goudra from the University of Pennsylvania.

DR. LITMAN: Ron Litman, pediatric

anesthesiologist, University of Pennsylvania and medical director of the Institute for Safe Medication Practice.

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

DR. ZACHAROFF: And once again, I'm Kevin Zacharoff. My background is anesthesiology and pain medicine, and I am faculty and clinical instructor at the Stony Brook School of Medicine in New York.

DR. ZELTZER: Hi. Lonnie Zeltzer, distinguished professor of pediatrics, anesthesiology, and psychiatry, head of pediatric pain and palliative care at University of California, Los Angeles.

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

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

DR. KAYE: Good morning. I'm Alan Kaye. I'm professor, program director, and chairman at LSU School of Medicine in New Orleans.

DR. TERMAN: I'm Greg Terman. I'm professor of anesthesiology and pain medicine and the graduate program in neurobiology at the University of Washington in Seattle, and director of the acute pain service at the University of Washington Medical Center.

DR. ALEXANDER: Good morning. My name is John Alexander. I'm a cardiologist and professor of medicine and clinical researcher at Duke University.

DR. WARHOLAK: Good morning. I'm Terri Warholak, and I am a professor and assistant dean at the University of Arizona College of Pharmacy.

DR. HIGGINS: Jennifer Higgins, acting consumer representative for AADPAC.

MR. O'BRIEN: Joe O'Brien, patient representative and president of the National Scoliosis Foundation, and a sixth-time spinal fusion patient.

DR. HERRING: Good morning. I'm Joe Herring. I'm a neurologist in the clinical neuroscience group at Merck and industry representative to the AADPAC.

DR. ZACHAROFF: Thank you.

For such topics as those being discussed at today's meeting, there are 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 the meeting has concluded. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I'll now pass it to Moon Hee Choi, who will read the Conflict of Interest Statement for this meeting.

Conflict of Interest Statement

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

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC, Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial

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

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 USC Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of new drug application NDA 210730 for oliceridine, 1 milligram per milliliter injection, submitted by Trevena, Incorporated for the management of moderate to severe acute pain in adult patients for whom an intravenous

opioid is warranted. The committee will also be asked to discuss the efficacy and safety data and benefit-risk considerations.

This is a particular matters meeting during which specific matters related to Trevena'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 the FDA's invited industry representative, we will like to disclose that Dr. William Herring is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Herring's role at this meeting is to represent industry in general and not any particular company. Dr. Herring is employed by Merck & Company.

We would like to remind members and temporary

voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. ZACHAROFF: Let's begin the meeting with FDA introductory remarks from Dr. Sharon Hertz.

FDA Opening Remarks - Sharon Hertz

DR. HERTZ: Good morning, Dr. Zacharoff, our committee and invited guests, additional invited guests here in our meeting room here today. Thank you all for coming, particularly those of you who've traveled from far and wide. We're here today to talk about what we refer to as an NME, a new molecular entity, a novel analgesic, which is exciting.

This product was studied as a 505(b)(1). We often talk about the (b)(2) applications, and we'll talk about that for tomorrow. But as a new entity, the

applicant is required to demonstrate safety and efficacy for the intended population, as well as any novel characteristics that they believe the product may carry.

You'll be hearing about two phase 3 studies and a safety study. You'll be hearing about data on cardiac effects and on respiratory effects. And we're going to ask you what that all means and what your interpretation of all this turns out to be and how that influences your decision on whether or not this product should be approved for marketing. It's intended for acute pain. It's parenteral. It's intended right now to be used in the post-operative period, so our questions and your responses will hopefully focus on that.

Some of the outcomes that are of interest with this product can be very difficult to demonstrate, and we're going to ask you to elaborate a little bit more on that as you talk about some of the safety for this product.

This is a novel class of analgesics. You're going to hear a lot about this, so I don't want to

belabor it too much right now. But this is a biased agonist. It's a G-protein biased ligand for the mu opioid receptor, and that property is intended to differentiate this product from the traditional full mu agonists.

So we have you here for what really I think is an exciting product, an exciting opportunity to discuss something novel, and I look forward to hearing your comments throughout the day. Thank you.

DR. ZACHAROFF: Thank you, Dr. Hertz.

Before we begin the applicant presentations, it's important to note that 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 nonemployee presenters, to advise the committee of any financial relationships they may have with the applicant, such as consulting fees, travel expenses, honoraria, and

interest in a sponsor, including equity interest and those based upon the outcome of the meeting.

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

We will now proceed with Trevena's applicant presentations.

Applicant Presentation - Maxine Gowen

DR. GOWEN: Good morning, Mr. Chairman, members of the advisory committee, the FDA, and members of the public. I'm Maxine Gowen, founding president and CEO of Trevena, and we're very pleased to be here today to discuss oliceridine.

Oliceridine, as we heard, is a new chemical entity with a novel mechanism of action that was designed to deliver the pain relief of a conventional IV opioid with fewer opioid-related adverse events, thereby improving the risk-benefit profile for patients who require acute IV pain therapy, and it's the first

new molecule in this class of drugs in decades.

Let me first provide some background on Trevena and the discovery of oliceridine. Trevena was founded in 2008 based on the discoveries related to G-protein coupled receptors or GPCRs. These concepts came out of the lab of Robert Lefkowitz at Duke University. Dr. Lefkowitz won the Nobel Prize in chemistry in 2012 in part for several of the ideas that we continue to advance today, including oliceridine.

We used to think that GPCR, like the mu opioid receptor, operated like a light switch and could be turned on by agonists like morphine and off by antagonists like naloxone. This meant that both the beneficial and adverse effects were pharmacologically inseparable.

Thus, the opioids, it was thought that the analgesic effects could only be obtained with associated opioid-related adverse events. We now know that these receptors are not light switches, but that they have distinct signaling pathways.

When an agonist like morphine binds to the mu opioid receptor, it stabilizes receptor confirmations

that couple to G-proteins and beta arrestins. And these protein-protein interactions trigger downstream intracellular responses. The protein coupling appears entirely responsible for analgesia, liking independence, and contributes somewhat to opioid-related adverse events.

Beta arrestin II coupling contributes to respiratory depression, nausea, and vomiting, as well as the attenuation of the analgesic response. This led to the hypothesis that if we could find a molecule that selectively engage G-protein while avoiding beta arrestin coupling, it could exhibit more favorable pharmacology than drugs like morphine. We hypothesize that such a molecule could provide the rapid and systemic analgesia of an opioid and reduce, but not eliminate, opioid-related adverse events, and this led to the discovery of oliceridine.

Oliceridine is a G-protein biased mu opioid receptor ligand with a novel mechanism of action designed to optimize mu opioid receptor pharmacology. It's a completely new chemical entity that is structurally distinct from conventional opioids. It's

not a derivative of opium such as morphine or hydromorphone.

IV opioids are an essential treatment option for the management of moderate to severe pain in the hospital and other controlled settings, and while optimizing multimodal therapy and ERAS protocols has reduced or eliminated the need for IV opioids for many procedures, there are still many settings where IV opioids are necessary when pain is more severe, deep, visceral, or longer lasting.

Last year, 45 million patients were administered an IV opioid in the U.S. hospitals, demonstrating the need for the high level of analgesia from this class of medicines. So why do we need another IV opioid to treat pain in the hospital?

Conventional IV opioids while extremely effective have many limitations, including adverse events like nausea, vomiting, and respiratory depression. And this is because conventional IV opioid options have narrow therapeutic windows. A narrow therapeutic window means the range of doses that are effective without leading to adverse effects is

limited, resulting in a small margin of error for dosing.

Safe and effective titration of morphine can be further complicated by the accumulation of active metabolites, which lead to unpredictability in the therapeutic responses as well as off-target effects. This will become important later in our discussion of efficacy endpoints.

While IV opioid analgesics are needed treatment options, we recognize that we are seeking approval in the backdrop of an opioid crisis. While diversion and abuse of IV opioids from controlled settings is relatively low, we believe that any new IV opioid should not expand the population exposed to these medicines or introduce a greater risk of abuse.

Thus, Trevena is requesting that oliceridine be a Schedule II product and carry the same mandatory restrictions as other IV opioids. It's also important to note that nonclinical data suggest that oliceridine can be reversed by naloxone in the case of an accidental overdose.

We don't expect the approval of IV oliceridine

to affect the opioid crisis for a few reasons. First, oliceridine is for short-term intravenous use only. It will be used only in a hospital or other controlled clinical setting. We do not expect approval of IV oliceridine to expand the number of patients exposed to IV opioids, but rather serve as a substitute for existing IV opioids like morphine. We're seeking approval for oliceridine because we believe it has the potential to improve care for patients who require IV opioid therapy.

We've studied oliceridine in more than 1800 individuals in 17 clinical trials, and I wanted just to highlight some of the unique features of our development program. While the FDA only requires a placebo control for our proposed indication, we also included IV morphine as an active comparator in our controlled studies to provide physicians with clinical context.

We also used PRN dosing, either through PCA or bolus, to reflect real-world practice and better informed clinical use. And finally, as the first molecule in this class with a potential safety benefit,

we set out to study respiratory safety using several approaches.

First, we conducted the experimental gold standard test for opioid induced respiratory depression, the ventilatory response to hypercapnia or VRH. Since there were no accepted clinical endpoints for respiratory depression in pain clinical trials, we evaluated a variety of different measures.

Across all placebo-controlled trials, oliceridine was superior to placebo, meeting the efficacy regulatory requirements for approval. The studies also showed that oliceridine is safe for its intended use. We've evaluated the full safe and efficacious dose range to support our dosing instructions. And as you'll hear later this morning from external experts, after thorough review, no clinically significant hepatic or cardiac safety issues were identified.

Across the clinical program, oliceridine delivered sufficient efficacy similar to morphine, establishing oliceridine as a potential alternative to conventional IV opioids. As the first company to study

a potential improved safety benefit over a conventional IV opioid, we learned a lot.

Although we did not achieve statistical significance in every analysis, what you will see today across multiple safety measures, studies, and interventions is supportive evidence that oliceridine is an incremental improvement over morphing. While we're not seeking a label claim, we have been encouraged by these findings and believe this evidence is supportive of our underlying hypothesis.

The proposed indication for oliceridine is as follows. Oliceridine is a G-protein biased ligand at the mu opioid receptor indicated for the management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted. The administration of oliceridine is to be supervised by trained medical personnel for acute use only within a hospital or other controlled clinical setting.

Based on our learnings and results from the clinical studies, our proposed dosing is as follows. Every patient should get an initial bolus dose of 1 to 2 milligrams. Subsequent doses may be given

approximately 10 minutes following the initial dose based on a patient's need and previous response to oliceridine.

Maintenance is generally achieved with either bolus doses of 1 to 2 milligrams every 1 to 3 hours as needed or as patient-controlled analgesia demand doses ranging from 0.1 to 0.35 milligrams as needed. And I'd like to be clear that the PCA dosing would be in this range, titrated up or down, dependent on patient need.

As you'll hear later in the presentation, we're not seeking approval for the 0.5 milligram regimen because it offered no efficacy advantage over the 0.35 milligram regimen. And lastly, we're proposing a maximum single bolus dose of 3 milligrams for patients with severe pain and a maximum daily dose of 40 milligrams. And this is based on the median of the top 350 patient exposures and allows for the wide range of doses captured in this group of patients.

Here's the agenda for the rest of our presentation. Dr. Mark Demitrack will review the efficacy and safety results from the phase 2 and 3 studies. Dr. Paul Watkins will then provide his review

of hepatic safety, followed by Dr. Robert Kleiman, who will provide a review of cardiac safety. Dr. John Violin will review the data on opioid-related adverse events, and finally, Dr. Gregory Hammer will provide his clinical perspective. We also have additional experts with us today to help answer your questions.

All external experts have been compensated for their time and travel but do not have an equity interest in Trevena. Thank you, and I'll now turn back the lectern to Dr. Demitrack.

Applicant Presentation - Mark Demitrack

DR. DEMITRACK: Good morning. I'm Mark Demitrack, chief medical officer at Trevena. I'll review the key efficacy and safety findings from the phase 2 and phase 3 studies.

The efficacy and safety of oliceridine is supported by two phase 2 and two pivotal phase 3, double-blind, placebo-controlled randomized clinical trials, as well as one large phase 3 open-label safety study. In all of our controlled studies, we went beyond the requirements for FDA approval for just a placebo control and included an IV morphine comparator.

Let me start with our phase 2a study, which treated 333 patients following bunionectomy. This study explores a range of fixed-dose strength of oliceridine, placebo, and morphine. While this paradigm does not reflect real-world use, it provides the clearest assessment of onset, magnitude, and duration of effects.

The study showed that fixed doses of oliceridine and efficacy for moderate to severe acute pain. This slide will show the results from the first dosing interval. Mean numeric pain intensity scores is the Y-axis and time on the X-axis.

Patients on placebo experienced little to no pain relief. Patients in the morphine 4-milligram group had significantly lower pain scores than placebo with an approximate 2-point change from baseline. The oliceridine 0.5 and 1-milligram groups had reductions in pain that were similar to morphine. The oliceridine 2- and 3-milligram groups had greater reductions in a dose-dependent manner, providing 5 to 6-point mean reductions by 5 minutes after dosing.

What this tells us is as you increase the dose

of oliceridine, you increase the magnitude of analgesia beyond that observed for morphine. The results from this study were incorporated into a PKPD model, which was used to inform the dosing regimens for our subsequent studies.

Study 2002 was our phase 2b study in 200 patients treated following abdominoplasty. The study used PRN dosing, which more closely reflects clinical practice and allows us to compare relative safety and tolerability.

The oliceridine regimens used a 1.5 milligram loading dose with either 0.1- or 0.35-milligram demand doses. The morphine regimen used the 4-milligram loading dose with a 1-milligram demand dose and was selected because it is commonly used in clinical practice. All regimens had a 6-minute lockout interval.

This slide will show the primary endpoint, the mean change in pain scores from baseline on the Y-axis over the 24-hour treatment period on the X-axis. Placebo patients experienced relatively little change in pain. Patients in the morphine regimen experienced

a significant reduction in pain scores compared to placebo. Patients in both oliceridine regimens also experienced significant reductions in pain scores compared to placebo, meeting the prespecified primary endpoint.

The improvements in pain were similar to morphine, supporting that PRN dosing would permit titration to similar analgesic efficacy with either oliceridine or morphine.

The results from our phase 2 studies were used to inform the design of our pivotal phase 3 randomized placebo-controlled studies. Following the FDA guidance, we evaluated both hard and soft tissue pain models so results could be generalized to the full range of acute pain settings where an IV opioid would be appropriate.

APOLLO 1 evaluated 389 patients after bunionectomy over a 48-hour treatment period. Prior to surgery, patients received a popliteal sciatic nerve block with local anesthetic, which was maintained using a continuous infusion via catheter until early on the first post-operative day. APOLLO 2 evaluated 401

patients after abdominoplasty over a 24-hour treatment period. Interoperatively, general anesthesia was used.

In both studies, patients were randomized in an equal ratio to one of three oliceridine regimens with different demand doses to a morphine regimen or to a placebo regimen. Consistent with the use of PCA in clinical practice, all patients received an initial loading, or bolus dose, followed by demand doses and supplemental doses as appropriate.

As in phase 2b, we again included the oliceridine 0.1- and 0.35-milligram demand doses. We also included a 0.5-milligram demand does to ensure that we evaluated the full safe and efficacious dose range for oliceridine. We used the same standard morphine regimen as in phase 2b.

All doses for the placebo regimen were volume-matched placebo solution. The studies used a monotherapy protocol, so multimodal analgesic therapy was not allowed. During the treatment period, patients could receive etodolac 200 milligrams every 6 hours for rescue pain medication if the study medication provided insufficient pain relief.

Next, I'll discuss some considerations for analyzing the efficacy of an IV opioid in the context of PRN dosing where patients self-administer their study medication. This is important because this morning, we will present data on our primary endpoint, which difference from the analysis presented by the FDA in their briefing materials.

Most treatment paradigms for opioid analgesics recommend that patients receive the amount of opioid they need to achieve adequate pain relief and no more than is necessary to achieve this treatment outcome. Considered from this perspective, it is our view that it is the sufficiency, not the magnitude, of efficacy that is most clinically relevant.

Consequently, any symptom relief that is greater than adequate should not really be considered a benefit; rather, this more accurately indicates that a patient is receiving an unnecessary exposure to an opioid, and therefore is more properly considered a risk.

To that end, clinical outcome assessments and treatment decisions that are based solely on magnitude

of pain score reductions tell only part of the story. In fact, such approaches may unintentionally bias towards treating patients with more opioid medication than they may actually need. This is particularly relevant for an opioid like morphine, which has active metabolites where an endpoint focused purely on magnitude may inadvertently credit efficacy at the expense of tolerability.

Therefore, we chose to base our primary outcome on a treatment responder endpoint that considers measures of both efficacy and tolerability, and therefore was less likely to consider overtreatment as a benefit.

The FDA guidance document for analgesic indications from 2014 acknowledges that responder analyses are appropriate primary efficacy endpoints. The guidance points out some advantages, including the fact that these outcomes may be easier for clinicians to interpret. Also, they can greatly mitigate the problems of missing data.

Thus, our treatment responder primary efficacy endpoint in our phase 3 studies was selected with both

clinical relevance and the FDA guidance in mind. The FDA expressed their agreement with our approach in our phase 2b meeting minutes. In those notes, they specifically said the division has no objection to use of a responder rate as an endpoint. However, the sponsor must incorporate those patients who discontinue into the analysis as non-responders.

We incorporated FDA's feedback into our treatment responder definition. A patient was considered a responder if they met all four of the following criteria. The patient had to experience at least a 30 percent improvement in sum of pain intensity differences or SPID. Stated clinically, a 30 percent reduction of the average baseline pain score in the APOLLO studies translates to an approximate 2-point reduction in SPID, which is recognized generally as a clinically meaningful change.

Other components of the responder definition are measures that reflect the sufficiency of analgesic effect. Responders had to complete the treatment period without use of rescue pain medication, without early study discontinuation, and without reaching the

study medication dosing limit. If any of these criteria were not met, the patient was considered a non-responder.

A benefit of this method of outcome definition is that there is no imputation procedures needed for use of rescue medication or early discontinuation. The primary efficacy analysis to demonstrate efficacy was to compare each oliceridine regimen to placebo.

The primary analysis I'll present in the next slide incorporates analysis considerations that were requested by the FDA during the NDA review. Specifically, this analysis, which I'll show, takes into account the use of other concomitant analgesics that were used in addition to the protocol-specified rescue pain medication. Also, this analysis accounts for missing pain score data using multiple imputation. This analysis does not change the efficacy conclusions for our primary endpoint provided in our briefing document.

All oliceridine treatment regimens met the primary endpoint and demonstrated statistically significant analgesic efficacy in both phase 3 studies.

In APOLLO 1, all oliceridine regimens met the primary endpoint with a significantly higher proportion of treatment responders compared with placebo. In APOLLO 2, all oliceridine regimens also met the primary endpoint, demonstrating superiority over placebo.

In both studies, we confirmed our hypothesis that oliceridine reached the plateau in efficacy with the 0.35-milligram regimen. There was no clinically apparent advantage with the 0.5-milligram demand dose.

Compared to morphine, in both studies, the treatment responder rate was lower for the 0.1-milligram regimen. The 0.35- and 0.5-milligram regimens had responder rates that were not significantly different from morphine.

We also assessed the sufficiency of analgesia by evaluating a patient's need for rescue medication. The results for time to first use of rescue pain medication were consistent with the results of the primary endpoint. In both studies, all active regimens had lower rates of rescue than placebo, shown in red. The use of rescue was similar in the 0.35 and 0.5 milligram and morphine regimens. This provides

additional support for the conclusion that the 0.5-milligram regimen does not meaningfully increase efficacy beyond the 0.35-milligram regimen.

I'd like to discuss the clinical meaningfulness of two different approaches to analyzing efficacy. Our prespecified primary endpoint for treatment responders is focused on the sufficiency of analgesia. The FDA's preferred efficacy analysis uses SPID with LOCF imputation, which is focused on the magnitude of analgesia. These distinctions are important, and I'll explain them over the next several slides.

When evaluating efficacy, one consideration is change in pain score. We looked at this outcome categorically with at least a 30 percent improvement as indicating clinically meaningful pain relief. In a SPID analysis, pain is measured on a continuum. The higher the percentage change, the greater the benefit. We believe that measures of pain by SPID places a greater emphasis on the largest possible decrease in pain, and therefore may unintentionally reward overtreating pain, which is counter to efforts to

minimize opioid exposure.

The next considerations are all the clinically significant events that could detract from efficacy, where the study medication either provided inadequate analgesia or couldn't be tolerated. In the responder analysis we used, patients who met any of these criteria were considered non-responders.

For the SPID analysis, rescue medication use is imputed using last observation carried forward for the duration of the labeled dosing interval. Discontinuation of study medication for any reason, which we view as an important indicator of patient comfort, is not accounted for. Discontinuation for lack of efficacy is also handled with LOCF imputation, and discontinuation for an adverse event is handled using baseline observation carried forward imputation.

These endpoints capture valid but different aspects of analgesic efficacy. A treatment responder outcome quantifies sufficiency of analgesic effect, whether a patient is comfortable. A SPID analysis measures the magnitude of pain score reduction or the intensity of analgesia. In contemporary pain

management, we believe a responder analysis, which is focused on patient comfort, is a more clinically meaningful measure of opioid efficacy.

Let me show some examples for how we arrived at this conclusion. As has been mentioned, we are not recommending labeled use of the 0.5-milligram demand dose because we do not think it demonstrates any clinical advantages over 0.35 milligrams.

On this slide, I'd like to kind contrast the responder and SPID analyses and how they help to clarify why this conclusion makes clinical sense. When looking at SPID LOCF analysis or the magnitude, 0.5-milligram regimen looks about twice as efficacious as the 0.35-milligram regimen. However, when we look at the treatment responder rate, the use of rescue analgesia, discontinuation for lack of efficacy, patient dissatisfaction, and clinician dissatisfaction, the 0.35 and 0.5 regimens are virtually identical. Similar findings were observed in APOLLO 2.

Our interpretation of these data is that SPID is an incomplete picture of efficacy. By emphasizing magnitude, SPID favors higher opioid doses, even when

it offers no benefit to other aspects of efficacy for the patient. Thus, we contend that SPID as the primary measure of efficacy is misaligned with the clinical goal of minimizing opioid exposure.

This point can be further underscored by the analysis of numeric pain scores. On the left of the slide is a graph of the average pain score over 12 hours using the LOCF AND BOCF Imputations presented in the FDA's briefing book. Patients on placebo had the highest scores, while patients on morphine had the lowest. The NRS scores for oliceridine were dose-regimen dependent.

When we look at the difference between the point 0.35-milligram oliceridine and morphine regimens, shown in the yellow highlighting, we see that after 3 hours, morphine separates from oliceridine by about 1 to 1 and a half points. The FDA briefing document notes that this suggests morphine is more efficacious than the oliceridine 0.35-milligram regimen. However, when we look at the incidence of rescue medication of each regimen over 12 hours, as shown on the right of the slide, there was no difference between oliceridine

and morphine.

Therefore, the separation of the 0.35-milligram in morphine regimen in pain scores does not appear to reflect any additional magnitude of analgesia without any apparent clinically meaningful benefit since patients found the sufficiency of analgesia the same. The higher magnitude of efficacy with morphine may be related to the delayed onset of accumulating active metabolites. Similar findings were observed in the APOLLO 2 study.

To summarize our efficacy findings, oliceridine is the efficacious IV opioid for use in the hospital or other controlled setting. We have studied a broad range of single doses and dosing regimens throughout development to provide useful dosing instructions for clinical use.

All dosing regimens met the primary endpoint versus placebo in both pivotal phase 3 studies. The secondary efficacy endpoints support an analgesic dose range between 0.1 and 0.35 milligrams, and there was no added benefit with 0.5 milligrams. This is reflected in the range of dosing regimens we are requesting for

approval.

After an initial loading or bolus dose of 1 to 2 milligrams, analgesia can be maintained with a range of on-demand doses, 0.1 milligram being the lowest efficacious demand dose and 0.35 providing maximum efficacy. In clinical practice, physicians can select the demand dose that is most appropriate for the patient based on the severity of pain and the patient's response, and titrate within that range as appropriate.

I'll now review the general safety findings from the pooled APOLLO studies. This table provides an overall summary of adverse events by treatment assignment for patients in the integrated phase 3 APOLLO studies. Most patients experienced at least one adverse event during the study. No patients in the placebo group or the lowest dose regimen oliceridine group had an adverse event leading to discontinuation. The rate was 3 to 6 percent in the other active groups.

The rate of serious adverse events was low in all treatment groups. There were 5 SAEs with oliceridine, most of which were identified by the investigators as unrelated. All SAEs resolved without

sequelae.

The rate of severe AEs was 6 to 7 percent in the oliceridine group, 3 percent in the placebo group, and 9 percent in the morphine group. The most common severe AE was nausea. There were no deaths.

I'll now summarize the results from ATHENA, our phase 3 open-label safety study. The primary objective of the open-label ATHENA study was to provide a comprehensive safety exposure data set of patients receiving treatment with oliceridine for moderate to severe acute pain. A detailed assessment of safety outcomes observed in the ATHENA study is presented in our briefing book.

As an open-label safety study, ATHENA was conducted in more diverse clinical settings than those included in the controlled clinical trials, such as inpatient and outpatient hospital departments, ambulatory surgical centers, and emergency rooms. 768 patients were treated with oliceridine administered as needed by PCA or bolus. Multimodal analgesic therapy, excluding other opioids, was permitted as clinically determined by the treating physician.

As expected, the cumulative dose and duration of exposure varied widely based on the clinical circumstances of the patients treated. Compared to the phase 3 controlled APOLLO studies, the ATHENA patient population was older and had a higher burden of comorbidities. In fact, one-third of patients in the study were 65 years or older.

Nevertheless, as you can see on the slide, the pattern and type of safety and tolerability observations were similar to those observed in the controlled APOLLO trials. There were also no differences in safety outcomes between the bolus and PCA treatment conditions. No new adverse events signals were observed. Therefore, we conclude that the overall safety of oliceridine was shown to be favorable in this broader, diverse safety patient population with more comorbid conditions.

The FDA has raised two areas of interest during their review of our NDA, hepatic and cardiac safety. I'll invite two external experts to summarize these findings. Dr. Paul Watkins will discuss hepatic safety and Dr. Robert Kleiman will discuss cardiac

safety.

Dr. Watkins?

Applicant Presentation - Paul Watkins

DR. WATKINS: Thank you, Dr. Demitrack. And good morning. My name is Paul Watkins, and I'm a clinically trained hepatologist and professor at UNC Chapel Hill. I also direct the Institute for Drug Safety Sciences at the university, and I have a longstanding interest in drug-induced liver injury. I've been asked to summarize the liver safety analysis of the clinical trials.

This panel of experts independently performed causality assessment on the 22 clinical trial cases of interest, and it should be noted that all are recognized experts in drug-induced liver injury, and each has served for more than a decade on the causality assessment committee of the drug-induced liver injury network that is supported by the National Institutes of Health. Let me review our evaluation and conclusion of these events.

A standard way of evaluating liver safety in clinical trials is with a tool called an eDISH plot.

Each point on this graph represents a single patient in a clinical trial. What is shown along the X-axis is the peak serum ALT values observed over the course of the study in each patient, and along the Y-axis is the peak serum bilirubin.

These are the two most important biochemical parameters to assess liver safety. Each of these parameters is expressed as fold upper limits of normal on a log scale. The graph is further divided into quadrants by a vertical line corresponding to a value of 3 times the upper limits of normal for serum ALT and a horizontal line corresponding to a value of 2 times the upper limit of normal for serum total bilirubin.

In this graph of the 252 patients who received placebo in the phase 2 and 3 studies, you can see in the right-lower quadrant of the graph that there are 4 who experienced elevations in serum ALT exceeding 3 times the upper limit of normal, 1.6 percent of the population, indicating that there's a background of liver injuries in this patient population.

With morphine, you can see that there were

5 patients who experienced an elevation in serum ALT exceeding 3 times the upper limit of normal, also about 1.6 percent, again pointing to the background incidence of liver injuries in this patient population.

With oliceridine, there are more individuals in the right-lower quadrant, but this represents a similar percentage of the patient population, 2.2 percent, which is not statistically different from what was observed during treatment with morphine and placebo.

Importantly, no patients appear in the right-upper quadrant, that is no patients with serum ALT elevations experienced a rise in serum bilirubin suggesting liver dysfunction. There are two patients with high serum ALT values, which our panel did not believe were likely due to oliceridine, and details on these two cases are in the sponsor's briefing book.

The most notable liver events occurred in the open-label ATHENA trial where there were no comparator treatments. As you can see in the eDISH plot from the study, there is a similar distribution of peak serum ALT values, and only 1 percent of the patients

experienced an elevation in serum ALT exceeding 3 times the upper limit of normal. But there are 2 patients who appear in the right-upper quadrants, possibly suggesting liver dysfunction, and 1 patient who experienced a very high serum ALT value that was an SAE described as liver and kidney failure by the investigator.

Each of these cases experienced serum liver chemistry profiles characteristic of hepatic ischemia and not drug-induced liver injury. The first was an aortic arch repair in which aortic cross-clamping restricted lower body perfusion, which is likely to cause hepatic ischemia. The bilirubin elevation was likely secondary to hemolysis caused by the cardiopulmonary bypass.

The second was a hiatal hernia repair in which only 6 milligrams of oliceridine were administered, an amount simply too low to cause such a liver event.

The third patient had a total knee replacement and suffered greater than a 50 percent hemoglobin and hematocrit drop in the days post-op and also experienced renal failure consistent with

hypoperfusion. We did not consider any of the remaining liver events highlighted by the FDA as likely due to oliceridine.

I'd also like to point out additional relevant considerations. There was no preclinical liver safety signal. There was no relationship between the dose of oliceridine received and the liver events, and this was true at any level of cutoff of serum ALT. The oliceridine doses received were low and the duration of treatment generally too short to cause drug-induced liver injury.

Finally, there were qualitatively similar events in those patients receiving placebo and morphine. The hepatology panel concluded that the events observed during oliceridine treatment were consistent with the background incidence of liver events presumably related to perioperative medications used, surgical procedures, or other unknown common risk factors in this patient population.

In conclusion, it was the unanimous consensus of me and my colleagues that none of the liver events observed in the clinical trials were likely the result

of oliceridine treatment, and based on the available data, there is no evidence of a clinically significant liver safety signal associated with oliceridine treatment.

Thank you, and I'll now turn the lectern over to Dr. Kleiman.

Applicant Presentation - Robert Kleiman

DR. KLEIMAN: Good morning. My name is Dr. Robert Kleiman. I'm a cardiac electrophysiologist, and I'm the chief medical officer for eResearch Technology and consult extensively in the area of cardiac safety. I designed and analyzed Trevena's thorough QT study. I've also reviewed the data that I'll be presenting with a second cardiac safety expert, Dr. Peter Kowey.

As I'll show, an integrated review of the cardiac safety data shows that oliceridine poses no clinically relevant cardiac risk. There's no preclinical signal, minor QT effect only for the supratherapeutic dose in the thorough QT trial, and no QT prolongation in the phase 3 studies.

A comprehensive battery of preclinical cardiac

safety evaluations showed no signals of concern. First, oliceridine and its two major metabolites were evaluated for their effects on calcium, potassium, and sodium cardiac ion channels. And this slide shows the IC50 for each compound, which is the drug concentration that blocks 50 percent of the flow through the channel. Block of the hERG potassium channels is particularly important because that's what causes drug-induced QT prolongation and sudden death.

The two metabolites have absolutely no effect on hERG or other cardiac ion channels. For oliceridine, the hERG IC50 is 4.3 micromolar, which is 116 times greater than the maximum human exposure. Furthermore, there was no QT effect in the isolated rabbit wedge preparation or in cynomolgus monkeys at an oliceridine exposure 8-fold than the maximum human exposure.

Trevena performed a well conducted rigorous thorough QT study. 58 participants were randomized to receive all 4 treatments in random order. These were placebo, oliceridine 3 milligrams, the proposed maximum single dose, and oliceridine 6 milligrams, a

supratherapeutic dose, each administered by IV infusion over 5 minutes. And finally, an oral dose of moxifloxacin 400 milligrams as a positive control. ECGs were evaluated over 24 hours to look for possible acute and delayed effects.

This slide will show the primary results. The Y-axis shows the placebo-corrected change from baseline for QTc versus time on the X-axis. The change in QTc is the primary endpoint for all QT studies. The gray dotted line at 10 milliseconds illustrates the threshold of regulatory interest for thorough QT studies.

This isn't the threshold necessarily for clinical concern, as many widely used drugs have a QTc effect that crosses this threshold. Instead, it's simply the criteria for evaluating QT more closely in patient populations during phase 3. Moxifloxacin, shown here in green, produced the expected increase in QTc, demonstrating that the study was sufficiently sensitive to characterize oliceridine's QT effects.

The 3-milligram oliceridine dose, the proposed maximum single dose shown by the purple line, had no

clinically significant effect on QTc, and the 6-milligram supratherapeutic dose shown by the Blue line produced slight QT prolongation. The mean Cmax for the 6-milligram dose was 284 nanograms per milliliter, which is 3 times greater than the average Cmax in clinical use.

The QTc effect for the supratherapeutic dose of oliceridine is similar to that of a therapeutic dose for moxifloxacin as well as many other approved drugs. It is not uncommon to see a small QT increase with a supratherapeutic dose of a drug during a thorough QT study. However, in accordance with FDA guidance, this small QT effect with a supratherapeutic dose prompted enhanced ECG monitoring in phase 3.

The FDA recommended obtaining ECGs in phase 3 at baseline following the first dose, and then periodically at later time points to look for potential delayed effects on QTc. Trevena followed these recommendations by collecting ECGs in more than 1500 patients in phase 3 at baseline, after 1 hour to study acute effects, and every 24 hours to detect any potential delayed effect due to metabolite accumulation

that might not have been detected in the single dose thorough QT study.

As I'll show you, the ECG data from the controlled APOLLO trials showed absolutely no signal of the QT effect. First, this figure will show that the ECG sampling in phase 3 was adequate to rule out any delayed QTc effects, and the slide shows plasma concentrations of oliceridine and the 2 inactive metabolites following theoretical maximum dosing, which is a patient hitting the PCA button every 6 minutes.

By 24 hours, oliceridine and its metabolites are at or near steady-state levels. Therefore, the ECG collection at 24 hours was sufficient to detect any potential delayed QTc effects with repeat dosing. And here are the ECG results from the controlled phase 3 APOLLO studies. There were no meaningful differences in the incidence of clinically significant QT prolongation across any of the oliceridine, morphine, or placebo groups.

The two findings that would have been most worrisome are a QTc increase to greater than 500 milliseconds or a change from baseline more than 60

milliseconds. And as you can see, there's really nothing here. I think that these are very compelling data. They show that metabolite accumulation doesn't produce any delayed QT prolongation.

As for ATHENA, the ATHENA study was an open-label study, so there wasn't a control group. Dr. Kowey and I have reviewed the ATHENA ECG data in detail. After taking into account the confounding variables such as QT prolonging concomitant medications or very high baseline QTc values, we didn't see any signal of QT prolongation.

There were a few patients with QT prolongation, but most of them had QT prolongation at baseline, and none of them had ventricular arrhythmias. In fact, among the patients who didn't have QT prolongation, only one patient undergoing aortic valve replacement had a single short episode of non-sustained ventricular tachycardia, which is very common in patients undergoing cardiac surgery.

In summary, a comprehensive preclinical program revealed no QT concerns. The thorough QT study showed a small QTc increase only for the

supratherapeutic oliceridine dose. This finding is common in thorough QT studies, and the size of the effect was smaller than for moxifloxacin and many approved drugs. In phase 3, ECGs were collected to look for potential acute or delayed prolongation, and we saw nothing.

Though underlying mechanism for the slightly delayed QT effect in the thorough QT study is unclear, what's really important is that the control trials showed no clinically significant QT prolongation. Therefore, although the thorough QT study showed a small QTc effect for supratherapeutic dose, the phase 3 data show that this isn't clinically relevant.

The totality of the data showed that oliceridine poses no clinically meaningful risk for drug-induced ventricular arrhythmias. Thank you for your attention. I'll now turn the lectern back to the sponsor.

Applicant Presentation - Jonathan Violin

DR. VIOLIN: Good morning. I'm Jonathan Violin, and I'm one of Trevena's scientific cofounders and the senior vice president of scientific affairs.

Prior to joining Trevena in 2008, I was a fellow in the research laboratory of Dr. Robert Lefkowitz at Duke University. While there, my colleagues and I helped elucidate mechanisms of beta arrestin and G-protein coupled receptor biology and how biased ligands could potentially improve the benefit-risk profile of medicines.

The primary hypothesized benefit of oliceridine is that it would provide opioid-level efficacy and be able to attenuate, though not eliminate, the incidence of opioid-induced adverse effects like respiratory depression, nausea, and vomiting. As the first molecule in this class, there was no precedent for how to explore our safety hypothesis in the clinical setting. Therefore, we sought to evaluate the impact on safety in a variety of ways. including experimental models, clinically relevant events, interventions to address patient safety, MedDRA preferred terms, as well as novel endpoints.

Our goal was to try to identify dosing regimens that meaningfully reduced opioid-related

adverse events while also providing sufficient analgesic efficacy. That's why we included a number of secondary endpoints comparing oliceridine analgesia, safety, and tolerability to morphine.

Let's start with respiratory safety. For more than 40 years, the gold standard for evaluating opioid-induced respiratory depression has been the ventilatory response to hypercapnia or VRH. We incorporated this test in our phase 1 proof proof-of-concept study. It wasn't feasible to use VRH in later trials, so we used a variety of complementary endpoints to explore the clinical impact of oliceridine relative to morphine in phase 2 and phase 3. I'll start with our phase 1 pharmacologic proof-of-concept study.

We evaluated analgesia on respiratory effects using a randomized, double-blind, placebo-controlled crossover design. Thirty healthy volunteers were randomized and received study drug. As a crossover study, all volunteers participated in each of the 5 periods in a random order: placebo, a high 10-milligram dose of morphine, and oliceridine 1.5, 3,

and 4.5 milligrams as 2-minute Iv infusions.

During each period, the study used experimental models to evaluate drug-induced respiratory depression and analgesic effects in the same participants. To measure analgesic effects, we assessed pain tolerance using the cold pressor test. At baseline and various time points after study drug administration, participants place their hand in water cooled to 2 degrees Celsius and were asked to keep their hand immersed for as long as they could stand it, up to 180 seconds.

Analgesic effect was measured as pain tolerance, the amount of time participants could keep their hand immersed in the cold water. We assessed opioid-induced respiratory depression using the ventilatory response to hypercapnia. For this experimental model, participants inhaled 5 percent carbon dioxide to increase respiratory drive.

The percent change from baseline in minute Ventilation, which is the amount of air exchange per minute, was used to measure the drug's impact on respiratory depression. The study demonstrated that

oliceridine caused significantly less opioid-induced respiratory depression than morphine at doses providing at least as much analgesic activity.

The figure on the left shows the average change from baseline through 4 hours in pain tolerance on the cold pressor test. All active treatments showed greater pain tolerance than placebo. The 1.5 milligram oliceridine dose showed numerically less efficacy than morphine, and the 3 and 4.5-milligram doses showed numerically more.

The figure on the right shows the average change from baseline in placebo-normalized hypercapnic minute volume over the same 4-hour time period post dose. All oliceridine doses had a statistically lower impact on respiratory drive than morphine.

Thus, the 3 and 4.5-milligram oliceridine doses, which were at least as analgesic as morphine, produced significantly less respiratory depression. This finding confirmed our hypothesis that oliceridine substantially reduces, but doesn't eliminate, respiratory depression.

We sought to explore the impact of this effect

in our subsequent studies in the clinical context of PRN dosing. In our phase 2b study, we evaluated the incidence of clinically significant respiratory events. Our respiratory endpoint was called hypoventilation, defined as clinically apparent and persistently decreased respiratory rate, respiratory effort, or oxygen saturation. All events were ascertained using standard clinical monitoring in a blinded fashion.

As you heard earlier, the oliceridine regimens had analgesic efficacy equivalent to morphine. In that context, we observed significantly fewer hyperventilation events with oliceridine than morphine. The risk of a hyperventilation event was 71 percent lower for the oliceridine 0.1-milligram regimen and 42 percent lower with the 0.35-milligram regimen.

For the phase 3 studies, we established a formal protocol to closely monitor respiratory signs, symptoms, and interventions. Anesthesiologists and certified nurse anesthetists were trained to ensure that all relevant observations and all clinical interventions were systematically recorded. The studies were designed to quantify the incidence,

severity, and duration of the relevant clinical events.

Respiratory status was monitored at least every 2 hours or at least every 30 minutes during a respiratory event, again, in a blinded fashion. In our phase 3 studies, we prospectively defined respiratory safety events, or RSEs, in a similar manner to phase 2. The anesthesiologist or CRNA used their clinical expertise to observe and declare a clinically relevant worsening in oxygen saturation, respiratory rate, or sedation.

To capture an additional aspect of respiratory safety, we combined the incidence of RSEs with a cumulative duration of the events using a new composite index called the respiratory safety burden, or RSB.

RSB was calculated by multiplying the incidence of RSEs with their cumulative duration so it can be interpreted as the expected amount of time a patient would experience a respiratory safety event. RSB was prespecified as a key secondary endpoint in the APOLLO Studies. However, because this endpoint was new and had not been validated, it was not eligible for a comparative FDA labeling claim.

Finally, we also evaluated clinical interventions to address respiratory safety events, including supplemental oxygen dose and interruptions, and study medication discontinuations. RSB was numerically lower in all regimens compared with morphine in a dose-regimen dependent manner. However, none of the differences were statistically significant.

We believe this was caused, in part, by an unexpectedly lower incidence of safety events across all groups compared to phase 2. This slide shows that lower incidence of respiratory safety events in phase 3 and all study groups compared to the phase 2b study. The incidence of events was approximately 50 percent lower in phase 3 than in phase 2. We think this lower incidence is, in part, due to the more rigorous monitoring for respiratory safety in phase 3. With closer monitoring from anesthesiologists and CRNAs, fewer patients got into trouble.

To further evaluate respiratory safety signals, we pooled data on respiratory safety events and interventions across the two phase 3 studies and compared results to our phase 2b study. For this and

ensuing displays, we're only focusing on the range of on-demand doses we are proposing for approval, 0.1 and 0.35 milligrams.

Despite the lower event rates in phase 3, the relative risk reductions and respiratory safety events compared to morphine were consistent with the phase 2 data. The incidence of respiratory safety events was attenuated by 71 to 80 percent for the 0.1-milligram regimen and by 33 to 42 percent for the 0.35-milligram regimen.

The clinical relevance of the reduction in respiratory safety events is further supported by the consistency of the relative risk reductions in oxygen desaturations, dosing interruptions, and administration of supplemental oxygen. These were all consistent with those observed for the incidence of RSEs themselves.

Next, I'll review the results of our findings from phase 2 and phase 3 studies on nausea and vomiting. In the phase 2b study, there was significantly less nausea and vomiting among patients who received oliceridine than morphine. The incidence of nausea was 43 percent lower than morphine for the

0.1 milligram regimen and 36 percent lower for the 0.35-milligram regimen. For vomiting, the incidence was 64 percent lower than morphine for both oliceridine regimens.

Phase 3 results were consistent with the phase 2b study. The incidence of nausea was significantly lower in the 0.1-milligram regimen compared to morphine, and the incidence of vomiting was significantly lower for both the 0.1 and 0.35 regimens, 41 to 61 percent lower than morphine.

This slide summarizes the relative risk reductions for nausea and vomiting with oliceridine compared to morphine. If we look at the totality of results for nausea using the range of regimens we've proposed for approval, in the same way we summarize respiratory safety events, we see a consistent favorable safety profile for oliceridine compared to morphine.

Results were even more compelling with vomiting, which arguably is the more objective and clinically important measure since vomiting can result in postsurgical complications. The risk of vomiting

was between 41 and 64 percent lower for oliceridine than morphine. We saw a similar risk reduction in the use of rescue antiemetics supporting the clinical relevance of these findings.

I'd like to close my presentation with an overall benefit-risk assessment. Let's review what we've learned about the biased ligand hypothesis for oliceridine, and then put that into with the analgesic utility of oliceridine. We set out to test our hypothesis that oliceridine, which avoids the beta arrestin pathway, would provide similar analgesia and liking to an IV opioid while reducing but not eliminating respiratory depression, nausea, and vomiting.

The clinical results provide support for this hypothesis. In terms of analgesia, both phase 3 studies met the primary endpoint, demonstrating the efficacy of all oliceridine doses with similar efficacy to morphine the 0.35-milligram regimen. For abuse liability, oliceridine and morphine exhibited similar liking at equianalgesic doses. In terms of respiratory depression, by the gold standard assessment,

oliceridine reduced opioid-induced respiratory depression by about 50 percent compared to equianalgesic doses of morphine.

Despite insufficient power to meet the key secondary endpoint in phase 3, we observed reductions in both respiratory safety events and interventions in our controlled clinical trials that were consistent with the magnitude of improvement seen in phase 1 and phase 2. We also observed consistent reductions in nausea, vomiting, and the need for rescue antiemetics.

We acknowledge that not every analysis was statistically significant. However, we're encouraged by the promising indications of a clinically differentiated safety profile for morphine.

It's important to remember that these comparative endpoints weren't designed to support approval, but instead were intended to test clinical differentiation. As the first drug in this new class, we have learned a great deal, and our current findings provide insights into future study methods.

When we integrate this analysis of our ORAEs with our analysis of efficacy, we propose that all

oliceridine has demonstrated a positive benefit-risk assessment. Here, we frame benefit in terms of analgesic sufficiency, which is aligned with efforts to give patients only as much IV opioid as they need and no more.

Here we show the relative risk for the primary endpoint in terms of benefit and safety events and interventions in terms of risk. Estimates to the left of 1 favor oliceridine, and estimates to the right favor morphine. The 0.35-milligram demand dose was comparable to morphine in providing sufficient analgesia. The 0.1-milligram regimen demonstrated clear efficacy but slightly less than morphine.

Here are the relative risks for the key safety endpoints. In every case, for each regimen and each study, for each endpoint, we see a consistent signal of fewer safety events and interventions with oliceridine than morphine.

A reasonable question to ask is why is there a good reason to believe in the underlying hypothesis when only some of these analyses reached statistical significance? If the biased ligand hypothesis was not

true and there was no effect, the chart would look more like a coin toss. Some of the endpoints would favor oliceridine and others would favor morphine. But all safety measures are consistently favoring a safety advantage for oliceridine across our proposed dose range and across different studies, different types ORAEs, and the interventions to address them.

Another level of support comes from the consistency of findings across the two major types of ORAEs. The mechanisms by which opioids cause respiratory depression and nausea and vomiting are distinct. The safety endpoints related to respiratory effects are highlighted in light blue and those related to nausea and vomiting are highlighted in pink. The fact that oliceridine reduced both types of events associated with the beta arrestin pathway further support the clinical differentiation between oliceridine and morphine.

In sum, we believe that the relative magnitude of benefits and risks supports a positive benefit-risk profile for oliceridine. Thank you for your time. I'll now turn the lectern to Dr. Gregory Hammer to

provide his clinical interpretation of the results.

Applicant Presentation - Gregory Hammer

DR. HAMMER: Good morning. My name is Greg Hammer, and I'm a professor of anesthesiology, perioperative, and pain management, and pediatrics at Stanford. I manage adult and pediatric patients with congenital heart disease. I was an investigator in the ATHENA study, and I'm here to provide my clinical perspective on oliceridine.

Most of the patients I see undergoing surgery and admitted to the hospital need IV opioids for post-operative pain management. Achieving high-quality pain relief without side effects is challenging. We have made progress in post-operative pain management. We have implemented multimodal non-opioid therapy and techniques employing local anesthetics. On the other hand, we haven't made any significant improvements to IV opioid therapy over the last several decades.

What I find really exciting is that biased ligands have been engineered to target pain with the efficacy of opioids but with fewer adverse effects. What we need to keep in mind, though, is that progress

with this new generation drugs will be incremental. Therefore, we need to embrace step-wise progress with improved compounds that represent a significant advance even if they're not perfect.

In my opinion, oliceridine is the first step in an exciting biased ligand analgesic discovery process. I have looked at the safety and efficacy data from the clinical studies. I have also had personal experience with oliceridine the ATHENA study. I am convinced that this novel drug represents an important incremental advance in IV pain management.

Oliceridine provides opioid-level IV analgesia with an improved safety and tolerability profile. I'd like to discuss some of the improvements in safety that I think are most important.

We all know that IV opioids are associated with adverse events, nausea and vomiting being the most common. Nausea and vomiting are not life threatening, but these side effects can be really awful for patients. There are data indicating that surgical patients would rather have pain than nausea and vomiting.

We may be able to mitigate nausea and vomiting to some degree with antiemetics. The antiemetics we use unfortunately have their own side effects and they don't always work. Up until now, we have assumed that achieving IV opioid-level pain control meant that our patients would be at risk for nausea and vomiting. However, the clinical studies show that oliceridine caused less nausea and less vomiting than morphine.

In the phase 2b study, 3 and 4 patients receiving morphine had nausea. Oliceridine reduced the incidence by 35 to 40 percent; 2 and 5 morphine patients vomited, which oliceridine reduced risk by 64 percent. In the phase 3 studies, 2 and 3 morphine patients experienced nausea, and oliceridine reduced the incidence by 15 to 40 percent. 1 and 2 patients taking morphine vomited, which oliceridine reduced by 40 to 60 percent.

Oliceridine does not completely eliminate nausea and vomiting. I think it's safe to say, though, that oliceridine reduces the risk of nausea and vomiting substantially. This is a clear advantage over the IV opioids we are currently using.

The most concerning adverse event with opioids is respiratory depression. We address this risk proactively by titrating IV opioids gradually to effect. The problem with conventional IV opioids is there narrow therapeutic window.

When we overshoot with dosing and the patient starts experiencing respiratory signs or symptoms, we often have to discontinue the opioid. We then have to increase supplemental oxygen administration or initiate high-flow nasal cannula therapy, or even continuous positive airway pressure. Occasionally, we may need to administer naloxone and positive pressure ventilation or even perform tracheal intubation. We then have to call a rapid response or code blue and transfer the patient to the intensive care unit.

We clearly need to reduce the risk of respiratory depression as much as possible. One of the most exciting properties of oliceridine is that it significantly reduces opioid-induced respiratory depression. The ventilatory response to hypercapnia test is gold standard for respiratory depression.

The ventilatory response to hypercapnia test

is the gold standard for respiratory depression. The oliceridine phase 1 of ventilatory response to hypercapnia and opioid-induced respiratory depression was impressive. This study provides the cleanest data on the benefit of oliceridine because it directly measured ventilatory response to CO2 with oliceridine versus morphine.

When we compare apples to apples with the oliceridine doses that were eqianalgesic with morphine, oliceridine caused 50 percent less depression of respiratory drive than morphine. Once the reduced impact on respiratory drive of oliceridine was established, the purpose of the respiratory safety measures in phase 2 and 3 was to see what the potential clinical impact would be.

The clinical observations in phase 2 and 3 studies were consistent with the results of the ventilatory response to hypercapnia study. In the phase 2b study, 1 and 2 patients on morphine had a hyperventilation event. Oliceridine reduced the incidence of hyperventilation events between 40 and 70 percent. In the phase 3 studies, 1 and 4 morphine

patients had a respiratory safety event.

Oliceridine reduced the incidence of those events by 33 to 80 percent; 1 in 4 patients taking morphine had their PCA button taken away from them due to respiratory safety issues. The two oliceridine regimens being considered for approval reduced the need for intervention between 40 to 80 percent.

I believe these findings are very important from a clinical perspective, so let's turn to dosing. Whereas the dosing regimens in the clinical trials were fixed, dosing in clinical practice will of course be more flexible. Following an initial loading dose, analgesia can be maintained with demand doses in the range of 0.1 to 0.35 milligrams.

In clinical practice, we would give a loading dose and choose a starting demand dose for the PCA depending on the clinical circumstances. For example, if we have a fragile patient or patient who has been sensitive to opioids in the past, we might choose a smaller starting dose such as 0.1 milligrams. We might choose the same dose for a patient with a history of post-operative nausea or vomiting or if the surgical

procedure was relatively minor.

Since the patient can use the PCA to dose themselves, we might see how they are doing early on with the low-demand doses. For larger patients or those undergoing more major operations, we would generally choose a higher dose. In all cases, we would titrate as needed.

In summary, IV opioids are necessary medications with many safety liabilities. This committee has met probably a dozen times just in the last few years to discuss products and programs intended to try to make opioids safer. Any effort to improve opioid safety is important, but we ultimately need to make the underlying analgesic molecules inherently safer.

Oliceridine is the first IV opioid that is engineered to reduce adverse events. This is an important first step. At the same time, we should acknowledge that oliceridine is not a perfect drug. It reduces the rates of respiratory events, nausea, and vomiting compared to morphine in the context of clinically equivalent analgesia, but it does not

eliminate adverse events altogether or reduce drug liking.

We all want to get to a place where we can have medications with opioid-level efficacy, minimal adverse effects, and no risk of abuse. I hope and believe that we'll get there, but we should not let the perfect be the enemy of the good. Any incremental improvement in opioid safety should be embraced.

Thank you. I'll now turn the lectern back over to Dr. Violin.

DR. VIOLIN: Thank you, Dr. Hammer. Before we take your questions, we'd like to take a minute to put our data in the context of the questions the FDA has posed to you.

First, is there substantial evidence of efficacy for oliceridine for the proposed indication? Yes. Oliceridine has demonstrated efficacy in every clinical trial, including pivotal phase 3 studies. Oliceridine has demonstrated comparable analgesic efficacy to morphine.

Secondly, is the safety profile of oliceridine adequately characterized? Yes. In terms of the safety

database, we've studied oliceridine in more than 1800 individuals in our 17 clinical trials. In the context of PRN dosing, where patients received only as much opioid as they needed, the 350 patients who received the highest cumulative dose and longest treatment will determine the maximum daily dose, which we proposed to be the median of 40 milligrams per day.

In terms of hepatic safety, an expert panel concluded that there was no evidence of a clinical safety issue with oliceridine. The noted hepatic events appear to be background incidents in the underlying patient population.

In terms of respiratory safety, certainly there's no greater safety risk with oliceridine than morphine. Rather, every endpoint we've measured throughout development is either numerically or statistically better than morphine. Definitively proving a safety benefit was never contemplated as an approval requirement. Nevertheless, we're encouraged by the uniformly consistent relative risk reductions for opioid-induced respiratory depression in the phase 1, phase 2, and phase 3 studies compared to morphine.

In terms of QT prolongation, two external experts agree that our ECG sampling in the phase 3 studies was sufficient to conclude that there is no clinically meaningful risk for drug-induced arrhythmia.

Third, in terms of the impact on public health, we know that oliceridine is only for acute use in a controlled setting and only for patients who require IV opioids to manage their pain. Oliceridine is intended as an alternative to conventional opioids, not to increase the number of patients who receive opioids.

We do agree with the FDA that oliceridine has similar abuse potential to morphine and have proposed Schedule II labeling to provide the utmost control of oliceridine's distribution and use.

Finally, regarding approval, oliceridine has met the regulatory requirements. Efficacy was demonstrated in two pivotal trials and the safety has been characterized in over 1800 individuals. Well beyond the requirements for approval, the totality of data suggests two things. First, oliceridine works and is an appropriate substitute for Iv morphine.

Secondly, the oliceridine safety and tolerability profile represents an incremental but important improvement over conventional IV opioids.

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

Clarifying Questions

DR. ZACHAROFF: So we will now have the opportunity for the panel to ask clarifying questions to Trevena. Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter.

Dr. Goudra?

DR. GOUDRA: Dr. Goudra from Penn medicine. Too many questions, but I'm going to ask all of them. In reference to slide 33, could it be ceiling effect in terms of better efficacy at higher doses at 0.5 versus 0.35? I know it's not clinically significant in terms of QT prolongation or death -- sorry; not significant at clinical doses, but could it be a problem in toxic doses like tricyclics?

The follow up to that question is patients with long QT syndrome used with other drugs, which

prolong QRS like ondansetron, should it be a problem or should we be more cautious?

The last question is just because it is slightly better than morphine, should that be a good reason to use it?

DR. VIOLIN: So three important questions. I'll answer the first, and then I'll ask Dr. Kleiman to answer the second, and then Dr. Hammer to answer the third.

With respect to a ceiling effect for efficacy, no, we don't think there's a ceiling effect. In fact, when we give patients higher doses of oliceridine as we did in phase 2 bunionectomy study -- in fact, let's bring up the core slide for the first dose in study 2001, please.

What we see is that when we get up to doses of 2 and 3 milligrams of oliceridine, patients can go from a 7 out of 10 pain score, so severe pain, to an average of 1 in 5 minutes. Certainly it's higher than the 4-milligram dose of morphine, but that's the sign of a very powerful analgesic.

So the key thing to remember in the phase 3

studies is that because this was PCA dosing, patients titrated their own cumulative dose. They chose to give themselves the dose that they achieved. Certainly we think that had they dosed more frequently, they would have achieved more efficacy. But they were able to titrate themselves to comfort, we think, to the same extent that they did with morphine.

For the second question regarding QT prolongation, I'd like to ask Dr. Kleiman to step to the podium.

DR. KLEIMAN: Dr. Robert Kleiman. The question I think you posed was although the therapeutic dosing of oliceridine doesn't pose a significant QT risk, what about if there is a supratherapeutic dose, or an accidental overdose?

We have two different pieces of evidence there. First, for the parent compound, which is the one that appears to be active at the hERG channel, the thorough QT study showed that even with a supratherapeutic exposure about 3 times higher than what you'd see with a clinical dosing, you have a very negligible QTc increase, one that would not be

clinically significant.

In terms of the two metabolites, first, neither of them has any effect on hERG whatsoever or the other ion channels studied. At least at the steady-state levels following accumulation with multiple dosing, we don't see any QTc effect.

Now, can we go beyond the exposures that have been tested to understand what would happen in even higher levels? No, not safely. But given that there's nothing, there's no QT signal at steady state in the phase 3 ECGs, I really don't think there's any strong evidence to suggest that we should have any concerns about that.

DR. GOUDRA: What about using patients with long QT syndrome and with drugs which cause QT prolongation?

DR. KLEIMAN: That's a good question. In general, when you have a drug that has a greater than 20-milliseconds QTc increase, you would expect to want to mitigate its effects by limiting concomitant use with other QT prolonging drugs or in long QT syndrome.

For a drug with an negligible but just above 10-millisecond upper confidence bound, I think I would probably worry about using it in some with congenital long QT syndrome just because we don't know how a particular individual with a genetic susceptibility would respond. I don't have any particular concerns in the case of the approved drugs such as ondansetron, that also have modest QT prolongation effects.

DR. VIOLIN: If I could add one point, Dr. Kleiman, keep in mind that the ATHENA study, 768 patients received oliceridine in the context of usual care. So that meant they got whatever multimodal analgesia, whatever anti-infectives, whatever was appropriate for their care. So we do have some experience with a lot of medications on board. And as Dr. Kleiman said, no additional signal that we found of concern in that study.

For the third question, I think it would be helpful for Dr. Hammer to describe why oliceridine we think should be improved.

DR. HAMMER: Greg Hammer, Stanford. I would not, as you characterize in your question, personally

think or represent that oliceridine is just a little better than morphine. I think that it is a crucial first step toward more highly-targeted therapy with a chemically engineered molecule that has minimal, if any, effect on the beta arrestin 2 pathway. And I think this is where we're going with highly-targeted therapies and medicine, and this is the first step. And I think if this drug does not go forward, it's going to have a very profound impact on research and development in this area.

But at least as importantly, I think the ventilatory response to hypercapnia tests, which used a gold standard test for analgesia and represents the gold standard test for respiratory depression, showed extremely impressive results compared to morphine. I think the drug has a significantly better safety profile with regard to respiratory depression.

I would also say that all of the signals in the phase 2 and 3 studies represent arrows pointing in the same direction, and that is that there's significantly less nausea and vomiting, as well as respiratory depression, in the clinical setting.

So I think for the reasons that the drug has performed extremely well in phase 1, phase 2, and phase 3 with respect to safety, and because this is really an important first step down the path of more highly-targeted opioid and analgesic therapy, I think that to me it's clear that the drug deserves to be marketed.

DR. GOUDRA: Thank you.

DR. ZACHAROFF: Dr. Litman?

DR. LITMAN: Good morning. This is Ron Litman. First, I do have a series of questions also that I'll just ask individually so you don't have to memorize them all. In Dr. Gowen's first presentation on slide CO-12, she said at the very bottom "not seeking label claims."

Can you just elaborate on what that actually means? I think it's going to help me frame the types of questions I'll ask and my approach to thinking about this today.

DR. VIOLIN: Sure. While clearly we believe that there is very consistent signal of benefit for oliceridine compared to morphine, we have not achieved

uniform statistical significance, and some of the endpoints we've used are not validated. So that means we are not seeking a label claim. Perhaps in the future we'll be able to study it further and establish a label claim for comparative safety.

DR. LITMAN: So you mean a label claim saying that you're not going to ever say that this drug is safer than morphine.

DR. VIOLIN: That correct. But for approval, I think you have a difficult job, which is not just did this meet a statistical hurdle on a validated endpoint to merit some language in the label, but integrating everything that we've shown for oliceridine, does this drug look useful and safe? And that's not really a statistical question --

DR. LITMAN: Right.

DR. VIOLIN: -- that's have we characterize this adequately that you would feel comfortable using it in patients.

DR. LITMAN: But all the presentations since then have
basically focused on its relative safety to morphine.

But at the same time, that's not what you're seeking.

DR. VIOLIN: Correct. So there are really two goals of the development program. One, meet the criteria for approval, demonstrate efficacy, and characterize safety and tolerability. So all the primary endpoints compared efficacy versus placebo and have always been positive in every study.

Then safety and tolerability of course is a more holistic assessment. That's something that of course you need to consider. But given that the scientific hypothesis was about comparisons to morphine and because, of course, morphine is important for you to understand clinically, how does this fit into clinical practice, we think that it's worth highlighting how oliceridine compared to morphine on all of these measurements.

DR. LITMAN: So speaking of which, can you pull up slide CO-20 again? It's a very impressive slide on the surface. And I wanted to ask, when you started giving higher doses of oliceridine and you got better pain control, were those equally potent to 4 milligrams of morphine, those doses?

DR. VIOLIN: When we think about potency, we think about what dose would match another dose of morphine. So for us, we think the potency ratio for a single dose is around 1 to 5; 1 milligram of oliceridine is equivalent to about 5 milligrams of morphine.

DR. LITMAN: So wouldn't it make sense then if you increased your morphine dose instead of having just a single dose, you would get the same results as the oliceridine 1, 2, and 3 milligrams?

DR. VIOLIN: Sure. Again, this was a fixed-dose study. We wanted to study PRN in phase 3, but let's look at the phase 1 study, looking at analgesia. There we looked at a 10-milligram dose of morphine. We wanted to go as high as we thought we could in our first-time-in-human study. Here, compared to a 10-milligram dose of morphine in this pain model, we were able to match or at least numerically beat that 10-milligram dose with 3 and 4 and a half milligrams of oliceridine.

The point for us is that we know that if oliceridine is dosed to higher levels, you can get

extremely powerful pain relief. In the context of PRN dosing, be it PCA or clinician administered, oliceridine really is titrated to effect, to help patients achieve comfort, not some specific magnitude of pain relief, and do that with hopefully beneficial safety and tolerability compared to morphine. And that's what we think -- all the arrows point that direction.

DR. LITMAN: That's a good lead into my next question. And that is -- if I could find it in my notes. Well, let's just go to the ventilatory test that you do, the VRH, who did that test? Where was that done in these patients?

DR. VIOLIN: That was done -- it's healthy volunteers done at a single center in a crossover study with a washout period between each randomized dose.

DR. LITMAN: Can you just give me some more details about that? Who actually -- I used to do these kinds of studies. It's really complicated, and it requires a lab that has a lot of experience. So could you just tell us about that?

DR. VIOLIN: Sure. The principal investigator

on this study was Dr. Webster, who's here with us today, so I'll ask him to comment on the study.

DR. WEBSTER: Hi. Lynn Webster, vice president of scientific affairs for PRA Health Sciences. Perhaps we should talk about your previous experiences, yes.

So your question is?

DR. LITMAN: Just more information about how these tests were done. Your lab has experience doing these?

DR. WEBSTER: Yes, we've been doing them for a few years; not for a long time. But we've gone through a process of learning how to improve the methodology. We bring subjects in. We expose them to carbon dioxide, and we look for those who are hyperventilators, hypoventilators. So we kind of enrich our population to try to identify a population that's going to be a good asset -- assay for us to use, and then we will randomize them into the study. So they're exposed.

You saw the bed. They're confined. They're in a bed, and they have like a CPAP machine.

DR. LITMAN: What are they doing while you're doing this?

DR. WEBSTER: Just sitting there. Just laying there.

DR. LITMAN: How do you control for their level of consciousness? One of the things we found is that depending upon who is talking to them -- and we ended up having to control them by making our patients watch a boring documentary.

(Laughter.)

DR. WEBSTER: No, we haven't done that, but we do have them in a quiet room. Lighting is always the same. It's quiet. No one's talking. They're acclimated to the environment. We actually do that in preparation for a few days. They have to put the mask on and go into the environment. So we don't have any changes. They're very well prepared for the actual test. Then they're breathing for about 5 minutes before we start collecting data.

DR. VIOLIN: And of course in this study, we're simultaneously measuring, or approximately simultaneously measuring, pain tolerance with a cold

pain test. So I'm not sure people would fall asleep with their hands --

DR. LITMAN: So you were doing this at the same time?

DR. WEBSTER: No, no. Well, during this same study, but there's a 5-minute interval of doing the VRH assessments. Then there will be a period of time before you'll do another VRH assessment. And during that interval, they may go do a cold pressor test.

DR. LITMAN: So VRH, cold pressor. I see.

DR. WEBSTER: Yes.

DR. LITMAN: Okay. Dr. Violin, just another question on CO-80, please. That was a really nice overall review of the risk profile. My main question here is when you're comparing it versus morphine, were those doses, again, equally potent?

DR. VIOLIN: So this was PRN dosing. So in each study arm, some patients clicked the PCA button a few times; some clicked it a lot. So there's a wide variety of cumulative doses. So whether or not it's equally potent is difficult to assess in that context. Was it comparable in getting patients comfortable and

achieving adequate pain relief? When we look at the primary endpoint, the rates of rescue use, patient satisfaction, clinician satisfaction, the answer is yes.

DR. LITMAN: Two hopefully real quick questions first for Dr. Watkins about the liver toxicity, which is concerning on the surface. And I wanted to ask, is there any feasible mechanism where this difference in the way that your drug causes analgesia would somehow selectively affect the liver?

DR. VIOLIN: I wonder if I should take that one since we've really investigated a beta arrestin function, and of course we talked to Dr. Watkins about this as well. There's really no evidence, no studies really, of what beta arrestin might do in the liver in preclinical studies, no evidence that there's anything that could cause any kind of drug-induced liver injury. So we really are swayed by the clinical evidence -- Dr. Watkins' review.

DR. LITMAN: There's no feasible evidence at the cellular level why it would have a propensity to cause liver damage over traditional opioids.

DR. VIOLIN: Nothing that you could point to, no.

DR. LITMAN: And the same thing with cardiac.

DR. VIOLIN: Correct.

DR. LITMAN: Just last, is there any evidence of those patients that you saw that had bumps in their livers that indicated that they got either increased dose or increased duration?

DR. VIOLIN: Of oliceridine?

DR. LITMAN: Yes.

DR. VIOLIN: No. In fact, as Dr. Watkins mentioned, some of these cases had very low doses of oliceridine. A couple of them had 2 milligrams of a cumulative dose of oliceridine. So there's absolutely no dose related effect. And again, as Dr. Watkins pointed out, we think instead the cases of note just reflect the underlying patient population.

DR. LITMAN: I have a problem with the underlying patient population because you're taking those cases out in isolation. You don't know whether or not all the other patients who got morphine or had liver disease or whatever, all the other things.

DR. VIOLIN: Maybe Dr. Watkins could comment on that.

DR. WATKINS: Paul Watkins, University of North Carolina, Chapel Hill. The possibility or the biological plausibility of oliceridine causing liver effects different from morphine was discussed amongst the experts and the relevant data was reviewed. And there was no mechanism identified that could account for this.

What was the other question? Sorry.

DR. LITMAN: I'm just a little worried about the dose or the duration effect. In fact, I'll just add one small thing to finish. Do you have any concerns about patients who are taking this longer than your study showed?

DR. WATKINS: There's no evidence to suggest longer term treatment would increase a concern about liver safety based on the data that we have.

DR. LITMAN: Thanks for indulging all my questions.

DR. ZACHAROFF: Thank you. Dr. McCann?

DR. McCANN: Thank you. Dr. McCann from

Boston. My question is on slide 53 for Dr. Kleiman. There's a big, I think, knowledge gap as to what you do with patients that have received ondansetron. In our particular practice, almost everybody gets the drug, and you're not asking to give this drug interoperatively. I think you're seeking to give it post-operatively, meaning most of the patients would have received a narcotic, and therefore would have received some ondansetron.

Then how do you reconcile starting this medication with the issue that some patients may get more than the 3 milligrams that you suggest in terms of prolongation of QTc?

DR. VIOLIN: As Dr. Kleiman steps to the podium, let me clarify a few points about our phase 3 study. In the APOLLO study, the pivotal efficacy studies, prophylactic antiemetics were not allowed because we wanted to isolate the effects on nausea and vomiting. But ondansetron was the rescue antiemetic, so if it helps, we can bring up the rates of that use in the APOLLO studies.

In the ATHENA study, again, that was care as

usual, and many, many patients received ondansetron and other antiemetics and other concomitant meds. And again, as Dr. Kleiman said, we really did not see any signal of concern for QT in that context. But I'll let him comment to that effect.

DR. KLEIMAN: You raise an excellent point. What happens to patients who are already taking QT prolonging meds or are going to get ondansetron, which is going to happen obviously. But if you take a look at what happens with the therapeutic, the top-range, single therapeutic dose of 3 milligrams, the mean Cmax 152 nanograms per milliliter, about 50 percent higher than the mean Cmax with clinical use, they don't have a significant QT effect. So adding ondansetron to that is not going to produce a problem.

Now, I can't tell you about amiodarone. You start with the QTc of 550, yes, your QTc is going to remain above 500. But for the drugs like ondansetron, I don't think there's any reason to think that a therapeutic dose will have any issue.

Now, that covers the parent. That covers the supratherapeutic exposure of oliceridine. How about

the metabolites? Despite the fact that they're inactive, they don't have any ion channel effects. You always worry about that. And the phase 3 data shows that at steady state, when they've reached whatever amount of accumulation they will reach, there's no QT prolongation. So I don't have a big concern about the modest QT prolonging drugs that are already out there and that patients will definitely be on.

DR. McCANN: Can you pull the information about the patients that got ondansetron for us?

DR. VIOLIN: Sure. Let's look first in the APOLLO studies, look at the incidence of antiemetic use. Again, prophylactic antiemetics were not allowed in APOLLO, as you can see in both APOLLO 1 and APOLLO 2. Pretty common use as a rescue; less frequent with oliceridine than with morphine, which of course supports the notion that oliceridine has better upper GI tolerability. But to your point, we've seen a number of patients receive ondansetron after receiving oliceridine.

When we look at the ATHENA study, again, when we look at concomitant antiemetics, we can see

serotonin antagonist, including ondansetron, were quite prevalent. And again, this was 768 patients. So we do think we've characterized the safety in that context.

DR. ZACHAROFF: Thank you. Dr. Zeltzer?

DR. ZELTZER: Lonnie Zeltzer, UCLA, and probably for you. Given that a different elk for efficacy was used in previous studies -- so it wasn't magnitude of pain reduction but rather reaching a certain criteria, 30 percent drop in terms of enough reduction, did you look at -- and I think you did from the materials -- patient satisfaction so that if they had a choice to undergo a similar surgery, having experienced your drug, would they opt to use that again? Because that will influence in clinical practice.

DR. VIOLIN: Right. So the question we asked of both clinicians and patients was satisfaction with the study medication. That was the wording of the question.

Here are the results from APOLLO 1, looking at the three oliceridine regimens, placebo, and morphine. And what you can see is lots of dissatisfaction with

placebo, as you can imagine. And that pattern markedly changes when patients receive oliceridine.

So the green bars here are patients who said they were either mostly or completely satisfied. The red bars are mostly or completely dissatisfied. And clinicians and patients had a very similar pattern, and we saw a very similar result when we looked at APOLLO 2.

DR. ZACHAROFF: Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. My question is more about demographics. I was struck by the APOLLO studies and the lack of men in those studies. And I'm wondering why there were so few. Page 43 of the background materials says that the 3002 study had only 3 men, whereas you had 398 females. I'm wondering how this would impact dosing, and I'm wondering if you did any gender comparative analyses.

DR. VIOLIN: Yes. The APOLLO studies were chosen as pain models. They're designed to reliably produce pain and reliably detect analgesic effects. So when we look at the small number of men in APOLLO, we really don't see any difference in performance of

oliceridine, but it's a small number.

A better assessment that we can rely on is from ATHENA, where, again, this was designed to model real-world use. We had much better balance of men. We had a lot broader demographics. For example, we had over 200 patients over the age of 65. We had other subgroups that are very important for us to study.

So to answer your question, I'll show what happens in ATHENA to males versus females. So here, we can't talk about efficacy. It's an open-label safety study. But we can talk about effectiveness. We're looking here, females in orange, males in blue. We look at the change in pain score 20 minutes after baseline. Very similar, a 2-point drop for both males and females. In the middle panel, when we look at discontinuations for adverse effects or lack of efficacy, they're low, very similar across sex. Then when we looked at adverse events by severity and serious adverse events, no real difference.

We could show you the same pattern looking at elderly and looking at various at-risk patients. So the ATHENA data gives us some comfort that when we

leave the confines of the randomized-controlled study and take this to a more real-world type use, the profile of oliceridine is conserved. So this is a really important question for us.

DR. ZACHAROFF: Dr. Solga?

DR. SOLGA: Steve Solga from Penn. Dr. Violin, I'm just looking for some clarification and some help. I read through both briefing packets quite carefully, but I'm still trying to understand the hypothesis and how it adapts to clinical data.

On the executive summary in the Trevena briefing packet, there's a non-parallel construction in the executive summary at the bottom where it says, "G-protein, semicolon, responsible for analgesia, semicolon, and partial contribution to ORAEs." And then for beta arrestin, it says "contributes to ORAEs and attenuation of analgesic response."

I wonder if the beta arrestin shouldn't read "partial contribution to ORAEs," not "contributes." And I don't understand the attenuation of analgesic response. I understand that G-protein is where the analgesia is, but I don't see, and I could not

locate -- and I didn't look up any of your references, but I could not locate in the briefing packets evidence for support for the claim that beta arrestin attenuates analgesic response.

DR. VIOLIN: Understood. I think in our effort to be brief, we probably unintentionally confused you. There's actually a rich published literature on this. It's all nonclinical data. The key finding -- this was studies begun by Laura Bond when she was a postdoc at Duke.

If you give morphine to mice that lack beta arrestin and you compare them to wild-type litter mates, what you see is, using a standard analgesic test, morphine performance as you'd expect. It provides a transient analgesic effect. And in the absence of beta arrestin 2, the effect is magnitude, it's increased, and prolonged.

That's consistent with what we know beta arrestin does. The reason it's called arrestin is it sticks to the receptor, the receptor of the cell surface -- the arrestin sticks to the receptor and prevents further G-protein coupling. So it's

essentially putting the brakes on the analgesic signaling.

DR. SOLGA: Okay. As a follow-up question, if you don't mind, CO-80, you said the clinical data support the hypothesis, and here we have similar efficacy and fewer adverse side effects.

Can you speculate what would happen if you looked at a lesser dose of morphine in this? I mean, after all, there are three different dose schedules of the study drug and one of morphine, so certainly you're not going to be surprised by that question.

DR. VIOLIN: No. Yes, and that's a challenge when trying to run these kinds of studies. In terms of what comparator should we use, we really wanted to focus on a clinically relevant morphine dose, something that's widely used, the 4-milligram loading dose; the 1-milligram on demand; 6-minute lockout. Certainly there are alternatives. There's an infinite combination of parameters you could use for morphine PCA. We wanted something that would be a very reasonable benchmark, and we wanted to be consistent across studies.

So we can't answer your question. We don't have data. But certainly if less morphine is available, you'd expect less efficacy and less adverse effects.

This I think gets to one of the questions related to magnitude versus sufficiency of efficacy, given the SPID analysis suggests that the 0.35-milligram dose really isn't doing the job that morphine can do. But then when we look at discontinuations, at patient satisfaction, at rescue use, it's really comparable.

So we look at those as clinical indicators that that 0.35-milligram regimen really would do the job of this morphine PCA regimen. But for the broader question, we don't have enough data.

DR. SOLGA: Finally, one more question if you don't mind. Naloxone is certainly the most important rescue medicine, and I was surprised by the absence of discussion of that in both of the briefing packets. As a mu opioid receptor antagonist, is it biased towards G-protein, beta arrestin, neither, or don't know?

Would there be any reason to expect it would

be less efficacious with this drug?

DR. VIOLIN: No. So we studied this preclinically. The way oliceridine works is binding the exact same pocket on the mu opioid receptor as morphine and naloxone. It binds competitively. It has a residence time of minutes comparable to morphine. And both in vitro and in rodents, we can very rapidly reverse the effects of naloxone -- sorry; reverse the effects of oliceridine with naloxone administration.

We've never had to -- no patient who's been taking oliceridine has naloxone, so we don't have clinical data. But the preclinical data we think is convincing that it would work should it ever be necessary.

DR. ZACHAROFF: Thank you. Dr. Terman?

DR. TERMAN: Thank you. I'm Greg Terman from the University of Washington in Seattle. I'm going to just make a couple comments and questions about the pharmacokinetics.

I like the idea, it being an IV medication, an opioid that works very quickly has a relatively short half-life compared to most of the other things,

certainly hydromorphone and morphine. And it looks like as you were doing your studies, you discovered that it was shorter lasting than you were expected.

This is related to study 1003 on page 85 with the hypercarbic ventilation study. And that's very interesting. I was surprised that you looked at area under the curve over 4 hours given the shorter half-life of the drug. And I wondered whether there was a time-dependent inhibition of the ventilation in hypercarbia that might have gone away a little quicker than morphine, and thus had a little less morphine-induced respiratory depression.

DR. VIOLIN: Sure. I'm going to show rather complicated slide that I think will address your question, and we actually think is quite compelling. When we look at the time course of analgesic activity in the cold pain test and respiratory depression on the VRH test -- so here, every time point is a repeated measurement; again, crossover design, to remind everyone, healthy volunteers.

So when we look at analgesic activity, let's think about time windows, in the first hour, the 3 and

4 and a half milligram oliceridine dose markedly outperformed the 4-milligram morphine. From hours 2 to 4, they're pretty similar.

When we look at respiratory depression, look at VRH response, in the first hour, those doses of oliceridine are causing a comparable effect to morphine. But remember, at those time points, there's twice as much activity for analgesia. At the later part of the 4-hour time window where the analgesic activity is very similar, significantly less effect with oliceridine than with morphine.

So you're absolutely right, the PK is important. But wherever we look across time, through hour zero through 4, oliceridine is showing a favorable balance of analgesic activity to respiratory depression.

DR. TERMAN: Thank you. That same slide, it looks like the first analgesic test was pretty quick for morphine.

DR. VIOLIN: Ten minutes.

DR. TERMAN: As you can see, the morphine analgesia is still headed up in that first and second.

Then that was true in your other pharmacokinetic; again, fast acting, shorter half-life than other drugs. I find that to be interesting.

The question came up in your PCA studies as to whether analgesic doses of morphine and your drug were equipotent and you said that it was difficult to test. And in some of the information, you said it kind of bad luck that there were active metabolites for morphine that made it difficult to assess later on after the initial few hours of what might be due to metabolite.

That is unfortunate, although certainly, other drugs could have been chosen as comparators that don't have that problem, things like fentanyl or hydromorphone. But the way in practice that I tell whether things are equipotent or not is asking the patient to tell me by the number of button pushes that they make.

In both of your phase 2 studies, the 0.1 dose, the patients were to hit the button on the average pretty much 4 or more times an hour. The 0.35 dose, they were to hit it, oh, somewhere in the 2.8 button pushes an hour. The 0.5, they hit it 2.1 or 0.2 doses

an hour. In the morphine, it was kind of 1 to 1.5 doses per hour.

I would interpret that as saying that your morphine dose was a little on the high side compared to your study drug. But I would also say that 1 milligram is exactly what I would have used if I was going to do this study. You may have been unfortunate in that these two clinical models that you chose, a bunionectomy on day 2 and the abdominal procedure, may just not have needed as much pain medicine. So your normal dose of morphine was a relative overdose on the PCA.

I'd be interested in your comments on that because that will be very relevant for the rest of the day in terms of my thinking.

DR. VIOLIN: I'd just like to clarify to make sure we're all on the same page with the terminology here. When we say potency, we're talking about the relative doses. When we speak of efficacy, we're talking about the level of effect, which for us is sufficiency of pain relief, getting patients comfortable.

The morphine PCA dose, again, we chose that regimen and we wanted to be consistent. We didn't want to have different morphine regimens throughout development. So we stuck with that regimen as one that's widely used that would be a good benchmark for the study and provide relevant comparisons for oliceridine. And we were really encouraged that in terms of getting patients comfortable, all these assessments of adequacy or sufficiency of pain relief, that 0.35-milligram regimen, very similar to morphine.

The fact that, as we showed, it looks like morphine patients were getting a higher SPID score and driving their pain scores lower, but no real difference in satisfaction, or discontinuations, or rescue use. It could be any number of factors.

We don't have data with other regimens. To us, at the end of the day, what we believe is that the oliceridine regimens we provide, we studied, have shown what we'd hoped to show. They work. They show very encouraging signs for safety and tolerability.

I think the final point, I'd actually like Dr. Hammer to comment on. When you think about these

regimens, how would you use them in clinical practice? Do they look like they would do the job in his patients?

DR. HAMMER: Greg Hammer. Stanford. I think the data, as you've just reviewed, show that the drug is effective and that patients who are allowed to push the button as many times as they want, or get rescue medication, or withdraw from the study have good quality pain control; that is they titrate themselves to comfort, and they're satisfied, and the physicians are satisfied, and so on. So I think that efficacy is unquestionable.

Remind me, John, what the rest of the --

DR. VIOLIN: I thought it would be helpful to hear how you would think about these regimens, the 0.1 regimen versus the 0.35 regimen, how this would fit into your practice.

DR. HAMMER: Well, as I said, I would give a bolus dose customarily prior to starting a PCA, depending on what opioids were on board. And then depending on the patient and the usual clinical parameters, including the surgical procedure, start the

patient on a low dose. So if it's a small patient, if we're dosing not on milligrams per kilogram, but just as a milligram dose, start a small patient with a small operation and/or a patient who's had opioid sensitivity in the past or a predominance of opioid adverse effects, I would start them on a low dose, like 0.1.

Again, I'm sure as the panel know, we would review the number of button pushes on the PCA and determine whether the patient was pushing the button often enough that it merited an increase in the PCA dose. So start with 0.1, depending on what other multimodal strategies are being used, and then titrate upwards. I think some patients would be fine with a dose of 0.1 as the PCA dose and other patients having more painful procedures, like a thoracotomy for example, especially if they're larger patients, would be titrated up. You might start that patient on 0.2 and titrate up to .03 or 0.35 as needed.

DR. ZACHAROFF: Thank you. Dr. Alexander?

DR. ALEXANDER: Thank you. John Alexander. I'm from Duke. My first questions are for Dr. Kleiman, and the first one's really simple. Who interpreted the

phase 3 APOLLO 1 and 2 EKGs that were done at 1, 12, and 24 hours?

A second question, which you can take right after that, is in CO-53, the peak effect on QT interval was at around 1 hour, which is substantially later than the PK effect of oliceridine. Do you have an explanation for this delayed, modest QT effect?

DR. KLEIMAN: Robert Kleiman. To take the first question, the phase 3 ECGs were read by the sites. They were not centralized, which, if anything, would have produced wider confidence intervals and more false positives.

I've looked at data on millions of ECGs, and when you compare psych readings, which means ECG algorithm measurements versus centralized measurements, the machine readings generate more false positives than false negatives. So it will exaggerate the number of outliers. In APOLLO, there was one, so if it exaggerated it, I really can't speculate on that.

I think your second question was the very interesting one. From a scientific viewpoint, I would love to know why the QT effect -- now there was a QT

effect immediately at 2 and a half minutes. It's just that it's a little bit higher for the supratherapeutic dose at an hour. And for an IV drug, the maximum concentration is clearly when you administer it, not an hour later.

So that first raised the question, maybe it's one of the metabolites. But first of all, the metabolites are inactive at hERG, which is what we wanted to know. And second, when you look at them at steady state of 24 hours, there's nothing there. So I can't blame it on the metabolites.

I could speculate, if you have a couple of hours, about alternative mechanisms for minor QT effect, but I don't think it's transient. I think the relevant point is with the therapeutic dosing, the evidence shows in the phase 3 ECGs, there's no QT effect. There's no signal of concern.

DR. ALEXANDER: Thank you. And then I have a couple questions that might be for Dr. Demitrack or somebody else. In the briefing packet, figure 29 on page 67, they outline the total doses received in APOLLO 1 and APOLLO 2. Do you have any information

about the timing of these doses, maybe relative to the one 24 and 48-hour EKGs?

Were they all given before 1 hour or how was the dosing spread out in those trials?

DR. VIOLIN: So dosing of course was variable because this is dosed PRN. In general what you see is an initial titration phase in the first hour, and then patients tend to click at a lower rate in this maintenance phase to maintain their pain relief through the duration of the treatment period.

DR. ALEXANDER: Okay. Then just one last question. If I look at the proposed dosing regimen, which is an initial bolus of 1 to 2, and then subsequent boluses of 1 to 2 milligrams every 10 minutes -- so I don't treat pain professionally, but I can see people getting a lot more than 6 milligrams in an hour.

In the range of patients who would get this drug clinically for the wide range of pain syndromes, acute pain syndromes that they'd be getting it, what do you think the maximal doses would be in 1, 3, or 6 hours? We know that in 24 hours it's 40 milligrams,

but could that all be within 3 hours, or how would that play out in practice?

DR. VIOLIN: The 6-milligram dose gets plasma exposures far higher than where we're seeing efficacy. So with 1 to 2 milligrams, again waiting 10 minutes after the first dose to begin titrating pain relief, it's really unlikely that patients are going to dose to an extremely high level.

To the extent that we worry about bolus dosing, we did evaluate that in ATHENA, where there was both PCA and bolus dosing. So that titration phase and the maintenance using exclusively bolus dosing was included in ATHENA. And as Dr. Kleiman said, we didn't see any signs of concern in that study for QT prolongation.

DR. ALEXANDER: Thank you.

DR. ZACHAROFF: Thank you. I have a few questions, which I'm going to keep brief for the sake of time. I just want to verify that the proposed indication is for the management of moderate to severe acute pain in adults in an institutionalized setting. That's correct?

DR. VIOLIN: Correct. So management of moderate to severe acute pain where an IV opioid is warranted. So you can imagine that that places it in the realm a controlled setting under the supervision of a healthcare professional.

DR. ZACHAROFF: But it could be a nonsurgical situation.

DR. VIOLIN: Yes, and we did study that in ATHENA as well.

DR. ZACHAROFF: Okay. That was my question.

Is there any data that you have with respect to transitioning patients to other medications after -- let's assume this was delivered by PCA, is discontinued? Can you give us any guidance about what to do, how long to monitor for respiratory depression, et cetera, et cetera, if we discontinue the PCA pump with oliceridine, and then we're going to give the patient let's say an oral or IM opioid medication.

DR. VIOLIN: This is where the lack of active metabolites and the relatively short offset, the half-life, really helps. The drug clears quite quickly, and all the pharmacodynamic effects we've ever

seen track very nicely with oliceridine concentration. So you can feel comfortable that within an hour or two after ending oliceridine IV, its effects are going to be washed out and patients can be transitioned to whatever usual care is.

That's how it was studied in ATHENA. Of course what the transition is, too, is highly patient and procedure dependent, and that's how it was treated in ATHENA.

DR. ZACHAROFF: Then just lastly, in addition to measuring patient comfort, was there any measurement or is there any data about functional impact, time to ambulation, time to discharge on patients who were given this medication as opposed to morphine?

DR. VIOLIN: No. Certainly we're interested in that, but because we needed to measure pain over 24 or 48 hours in the APOLLO studies, the randomized-controlled studies, that meant that patients were maintained on PCA until the end of the treatment period unless they discontinued. So that really didn't allow us to look at functional assessments.

DR. ZACHAROFF: Thank you.

Mr. O'Brien?

MR. O'BRIEN: Thank you. First I guess I want to thank Dr. Gowen and the entire Trevena team. As I indicated in the introduction, I am a 6-time spinal fusion patient. This last December, I had my sixth, which was a revision surgery from L1 fusion to the pelvic, requiring 14 pedicle screws and 4 rods, et cetera.

In that process, I would say that in terms of pain management post-surgery, due to respiratory depression, would, I would almost classify it as torturous in terms of the care, so that when I received this packet from the FDA three weeks ago, I was absolutely ecstatic at the opportunity to have this biased ligand targeted approach to hopefully be able to provide the analgesic effect without the adverse events.

That being said, I have to honestly admit when I got through at the end of the entire thing, I was somewhat underwhelmed and couldn't get to where I wanted to be in terms of spiking at the end zone because of what are results.

That being said, I have three questions, I guess, that I'd like to ask of Dr. Hammer, Dr. Demitrack, and Dr. Violin. First with Dr. Hammer, if I could just ask you, in terms of dosage, I was on 40 milligrams of oxycodone prior to the surgery, 11 months prior to the surgery. I was also diagnosed with sleep apnea.

Based on that, what would you give for a patient for dosage on oliceridine?

DR. HAMMER: Greg Hammer. Stanford. First of all, my empathy. I can only imagine what you've been through. When we get into patients who are tolerant and have been on high doses of oral opioids chronically, I think we're getting kind of off in the experimental land in terms of what works for the patient. Certainly, I would have to defer to the clinical circumstances and look at the whole patient in much more detail. And even then, we see a lot of interpatient variability in terms of what we need to do to provide analgesia after surgery in patients who are chronically exposed to opioids.

So I can't really give you an answer in terms

of how many milligrams of the drug. I would suggest under those circumstances, and we have other pain experts on the panel and so on. But we'd start at the higher end, I'm sure, and then titrate to effect. But I think that kind of management is complex, and it's tough to give a single answer.

MR. O'BRIEN: Thank you.

Dr. Demitrack, I was very intrigued with this concept of sufficiency versus magnitude as it relates clinically to the patient. To that regard with -- I think it was slide 20 or whatever it was. No, it wasn't 20; 22 or 20 -- wherever you were making the claim about magnitude.

Was there any patient recorded outcomes with that? Were there any questions of the patients, whether or not it made a difference for them to be a level 5 versus a level 3. How was that concluded in terms of patient satisfaction?

DR. VIOLIN: Why don't I just show the patient satisfaction scores? So let's look at APOLLO 1 first. So this was a questionnaire given for clinicians and patients separately, so looking at clinicians, patients

on the right. They were asked if they were satisfied with the study medication and rate it from mostly completely dissatisfied down to mostly they're completely satisfied.

What we see here is that compared to placebo, where in a both patients and clinicians, there were more patients that were dissatisfied than and satisfied, as with clinicians, all 3 oliceridine dose regimens and morphine had a very substantial effect on -- you see higher rates of satisfaction, lower rates of dissatisfaction. And again, we saw very similar results in APOLLO 2.

MR. O'BRIEN: Thank you. And actually, if you could keep that slide for a second.

DR. VIOLIN: Sure. Here we go.

MR. O'BRIEN: On the patient view, if I understand it, going from point 0.35 to .05 terms of satisfaction, the highest satisfaction is with 0.5. But you're not asking for 0.5, so now you go to point 0.35, which is actually less than the morphine.

Is that the way I read that slide?

DR. VIOLIN: It looks like it's numerically a

little lower. This is an APOLLO 1. We'll show APOLLO 2 in a moment. The satisfaction is numerically lower. The dissatisfaction is numerically also a little better than morphine, but I would call it as pretty close to each other.

MR. O'BRIEN: Okay.

DR. VIOLIN: But let's look at APOLLO 2 as well. Here, the magnitude is not as obvious when we look at placebo, but clearly when you see the decreased rates of dissatisfaction, particularly when we look at the patient view on placebo, that 0.35 regimen looks every bit as good as morphine.

MR. O'BRIEN: Thank you. Then my last question is for Dr. Violin, on slide 70, and 76, and others, but let's say slide 70. As I went through and I started to look at these adverse events -- and particularly, obviously in my case, I'm interested in respiratory distress, but even the vomiting and nausea.

You made a comment earlier, or someone had made a comment how important that is. And obviously if you've had spine fusion surgery, to be laying there, and the idea of being nauseous or vomiting is very

dangerous and worrisome. But it seemed to me as I went through this packet that every time I looked at adverse events, going from the 0.35 to the 0.5 seemed to be a significant increase in the adverse events.

Is that an observation that's correct? I guess I couldn't help but think that to link the emphasis on sufficiency, these adverse events somehow certainly related to one another.

DR. VIOLIN: You're correct. The adverse events tend to be a little more higher incidence with point 0.5 milligram compared to 0.35-milligram regimen. That's why we're not proposing approval for 0.5 because when we look at these measures that we think are linked to patient comfort, or adequacy, or sufficiency of pain relief, there's no real benefit of 0.5 above and beyond 0.35.

So if it does the job, just as well, but it has a trend towards higher adverse effects. In the patients we've studied, we don't see any added benefit of it. It certainly works. We think it would be an acceptable dose, but the 0.35 looks better. So certainly when you look at the SPID analysis, you get a

different view of things because that appears to be driving the intensity of pain relief higher, but it doesn't seem to be helping the patients more.

So that's why we think that 0.35 should be the high end of the dose range and the 0.1 milligram should be the low end of the dose range as the lowest effective dose. That would be a great place, as Dr. Hammer described, to start a patient. And many patients did just fine with 0.1 milligrams. We wouldn't want them to receive more oliceridine if they don't need it.

When we put that into context with what you described as -- it sounds like your view was that this doesn't look like we've achieved the holy grail, that we've completely eliminated these adverse effects. And we agree. We absolutely agree. I wish we had a drug that did that, but we don't. Instead, we believe, as Dr. Hammer elaborated, that this is an incremental but important improvement that we think can be valued by clinicians and patients.

MR. O'BRIEN: No, I understand that. My basic question for you actually as the original researcher on

this was why? Why is that happening? Why when you go from 0.35 milligrams to 0.5, do we see a marked increase in adverse events? Why is that happening?

DR. VIOLIN: Yes. With apologies, I'm going to show some rodent data. Let's look at the rodent therapeutic window slide, and this might help explain what we think is happening here.

MR. O'BRIEN: My concern is just for the patient. In case we happen to get into that realm, are we really endangering the patient at some point in time?

DR. VIOLIN: Yes. A very good point. But I will say that the 0.5-milligram regimen at no point looked worse than morphine. It just didn't have any additional benefit over 0.35. So we don't see anything wrong with 0.5. We just don't think there's any benefit of it above 0.35.

If we could run as many doses as we wanted in a clinical trial -- unfortunately, we can't. But here's what we think would happen, and we can do this kind of experiment in rodents. So here on the left, we're looking at analgesia in a rodent model of pain,

and we see in blue, oliceridine; gray is morphine, and you see nice dose-response curves for causing pain relief. And we know that oliceridine is more potent than morphine in rodents.

So to get a sense of how do these compare to each other, in the middle panel, we put these in terms of morphine-equivalent dose. So we normalize the dose to morphine, and now you see the analgesic effects overlay each other. So then in that context, of a morphine-equivalent dose, what happens to respiratory depression in rats? And here is where you see this improved therapeutic window.

So if you look at the gray curve, that's morphine. When you go to higher and higher doses of morphine, you see more and more, here, accumulation of carbon dioxide, so a physiological indicator of respiratory depression. And with oliceridine, it's the same receptor. You're engaging the same pharmacology, but you get to higher doses, higher analgesia, before you see that affect kick in. Eventually, when you get to high enough dose, oliceridine starts to look like morphine, and the potential benefit is lost, but it's

no worse. There's no new safety signal that's engaged here.

So really that's why we think steering to the lower end of the dose range, the 0.1 to 0.35 is best for patients and clinicians.

DR. ZACHAROFF: Thank you.

MR. O'BRIEN: Thank you very much.

DR. ZACHAROFF: Unfortunately, for the sake of time, we're going to have to stop here, and we're going to now take a 15-minute break, a hard 15-minute break. We'll start back up promptly at 10:45. And if I could please remind the panel members to remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any other member of the audience. We'll resume promptly at 10:45. Thank you.

(Whereupon, at 10:28 a.m., a recess was taken.)

DR. ZACHAROFF: Welcome back, and we are going to proceed. Before we go onto the FDA presentations, I want to give one panel member the opportunity to introduce herself who didn't have the opportunity

before.

Dr. Kilgore?

DR KILGORE: Yes. Good morning.

Dr. Elizabeth Kilgore, medical officer, FDA.

DR. ZACHAROFF: Thank you. And we will now proceed with the FDA presentations.

FDA Presentation - Elizabeth Kilgore

DR. KILGORE: Good morning. As you just heard, my name is Elizabeth Kilgore. I'm a medical officer in the Division of Anesthesia, Analgesia, and Addiction Products. This morning, I will provide an introduction and overview of the agency's presentations.

The order of presentations as shown in the agenda will be introduction and overview of the key issues for consideration at today's AC, which I will present, followed by a discussion of the abuse potential of oliceridine presented by Dr. Katherine Bonson of the controlled substance staff. Dr. James Travis, statistical reviewer will then discuss the agency's efficacy findings. Lastly, I will present safety and benefit-risk considerations for oliceridine.

You have heard detailed information regarding oliceridine earlier from the applicant. As noted, oliceridine is indicated for the management of moderate to severe acute pain in adult patients for whom an IV opioid is warranted. It is a new molecular entity G-protein biased opioid. And as the applicant has stated, they will not be pursuing approval of the highest dose of oliceridine. However, in the agency's efficacy and safety review and conclusions, we considered all three dose strengths studied in the phase 3 studies.

The applicant's clinical program included 11 phase 1 studies, 3 phase 2 studies, and 3 phase 3 studies. The main focus of FDA's presentations this morning will be the 3 phase 3 studies, which are designed to support the safety and efficacy of oliceridine. The smaller phase 2 studies were considered proof-of-concept studies by the agency and will not be discussed.

Dr. Travis will provide an overview of the two randomized, double-blind, placebo and active control studies in his talk, and I will provide an

overview of the open-label study when I discussed the safety findings.

In February 2016, oliceridine was granted breakthrough therapy designation primarily based on the suggestion of a better safety profile on clinically important opioid-related parameters in phase 2 studies. Between 2016 to 2017, FDA had several interactions with the applicant and discussed the data needed to support comparative safety claims, focusing on respiratory safety. As you will hear from Dr. Travis, FDA did not agree with the applicant's proposed respiratory safety endpoint. The NDA was submitted in November 2017.

The key topics for AC consideration include efficacy of oliceridine for adults with acute pain safety, findings to discuss safety database, hepatic safety, respiratory safety, QT prolongation, and overall benefit-risk of oliceridine for adults with acute pain.

Now, Dr. Bonson will discuss the abuse potential of oliceridine. Thank you.

FDA Presentation - Katherine Bonson

DR. BONSON: Good morning. My name is

Katherine Bonson. I'm a pharmacologist in the controlled substance staff, CSS, and I'm going to talk to you today about the abuse potential of oliceridine. For regulatory purposes, evaluation of a drug's abuse potential is considered to be a safety consideration, and under our 2017 FDA guidance, assessment of abuse potential of drugs, all CNS active drugs need to undergo an abuse potential evaluation during drug development.

Oliceridine is a mu opioid agonist that is proposed for the acute treatment of pain. Thus, it was necessary to conduct an abuse potential assessment for oliceridine. During drug development, CSS provided feedback to the sponsor regarding which abuse related studies in animals and humans would be required, as well as feedback on their appropriate design.

The applicant conducted the following abuse related assessment. We had them do receptor binding, which looks at where the drug acts neurochemically. We had them look at second messenger studies, the intracellular functioning. They also did behavioral studies using animal doses that provide plasma levels

equivalent to or greater than human therapeutic plasma levels.

So they looked at general behavior as well as two abuse related studies, drug discrimination, which evaluates whether the drug in question produces similar sensations to a known drug of abuse, as well as self-administration, which evaluates the rewarding properties producing reinforcement. Finally, we had them do a human abuse potential study in people with a history of drug abuse.

The receptor binding studies showed that oliceridine had high affinity for mu opioid receptors, similar to that of other opioids with abuse potential. However, in contrast, there was no significant affinity of oliceridine for other abuse related sites, including other opioid sites, either kappa or delta, or sites from GABA, dopamine, serotonin, cannabinoid, NMDA glutamate, or ion channels, or monoamine transporters.

In classic pharmacology, the binding of an agonist to a particular receptor leads to activation of a single second messenger system to amplify the response. However, investigations have shown that

there is often more than one intracellular signaling pathway associated with the receptor, and that each of these mechanisms may be responsible for different physiological or behavioral effects. Agonists will typically activate all of these second messenger systems after binding to the receptor, but some drugs will preferentially activate only one of them, and this is called biased agonism.

For the mu opioid receptor, there are two main signaling cascades, the G-protein pathway and the beta arrestin pathway. The G-protein signaling pathway is hypothesized to be responsible for opioid-induced analgesia. And in contrast, the beta arrestin signaling pathway is hypothesized to be responsible for opioid-induced respiratory depression and rewarding effects.

In vitro functional studies were conducted in human embryonic kidney cells expressing recombinant human mu opioid receptors. And in an assay of G-protein activation, oliceridine inhibited forskolin-stimulated cyclic AMP accumulation. So this shows that oliceridine activated that G-protein

pathway.

In an assay of beta arrestin activation, oliceridine did not produce a measurable formation of an active beta-galactosidase enzyme. So this shows that oliceridine did not recruit beta arrestin. In contrast, the mu opioid agonist, fentanyl, hydromorphone, and morphine each activated G-protein and beta arrestin pathways.

The ideal opioid for therapeutic purposes would produce analgesia without the risk of abuse potential and overdose, and this has been a research and drug development goal for over a century. But to date, all opioids that produce clinically relevant analgesia can also get people high when the dose is increased enough and can produce respiratory depression leading to death.

So mu opioids that function as biased agonists by only acting on G-protein and failing to recruit beta arrestin would appear to be desirable as pharmaceutical drugs.

Numerous candidate compounds that act as mu opioid agonists but have reduced recruitment of beta

arrestin compared to G-protein have been proposed to fulfill this role. However, oliceridine is the only drug that has been tested for its ability to produce analgesia, respiratory depression, abuse potential, and physical dependence in preclinical studies, as well as large-scale clinical trials that have been evaluated by FDA. The data from these studies will inform whether the lack of interaction with beta arrestin predicts an improved safety profile from mu opioid agonists.

The general behavioral studies that we had them do with oliceridine are conducted as safety studies, and they're done for all new drugs under development. In an evaluation of general behavior in rats, a 24-hour infusion of oliceridine at a high dose produced behavioral impairment, reduced food consumption, reduced body weight, and decreased forelimb strength relative to vehicle. In the rotorod test, which measures the ability of a rat to hold on to a slowly rotating rod, oliceridine and morphine both produced a similar impairment in motor ability.

We then had them do drug discrimination, and drug discrimination is an experimental method of

determining whether a test drug produces physical and behavioral responses that are similar to a training drug with specific pharmacological effects. Test drugs that produce response similar to the training drug with a known abuse potential are also likely to be abused by humans.

In the study that they conducted with oliceridine, rats were trained to discriminate morphine from vehicle, and then morphine was tested over a range of doses, and as expected, it produced full generalization to itself when the morphine cue was tested. And oliceridine over a range of doses also produced full generalization at the higher doses, 75 to 99 percent. These data suggest that oliceridine produces sensations that are similar to morphine, and this was expected of course because oliceridine is a mu opioid agonist like morphine.

We then had them do self-administration, and self-administration is a method that assesses whether a test drug produces rewarding effects that increase the likelihood of behavioral responses in order to obtain additional drug. That's called positive reinforcement.

Drugs that are self-administered by animals are likely to produce rewarding effects in humans, so the ability of a test drug to reduce self-administration is indicative that the drug has abuse potential.

In the self-administration study that they conducted with oliceridine, rats were trained to lever press for morphine as a training drug intravenously. And after self-administration of morphine was stable, animals were then allowed intravenous access to the following substances, which produced varying degrees of self-administration measured in terms of infusions per session.

So oliceridine at two higher doses produced 13 to 19 infusions per session, and morphine in contrast at higher doses produced 12 to 27 infusions, while placebo produced less than 5 infusions. These data show that oliceridine produces rewarding properties that sustain positive reinforcement similar to morphine. This again suggests that oliceridine has abuse potential.

We then had them do a physical dependence study with oliceridine, and this was conducted in rats

that received a continuous 14-day intravenous infusion of oliceridine at a range of doses, morphine, and vehicle. Observations were taken during drug administration and also during the 7-day drug discontinuation phase.

During the drug discontinuation phase, both oliceridine and morphine produced the following statistically significant changes. There's a decrease in food consumption, there was a decrease in body weight, and there were classic opioid withdrawal signs, including decreased locomotion, twitching, hunched posture, decreased muscle tone, vocalizing, aggression, and soft feces.

These data show that prolonged administration of oliceridine produces opioid withdrawal signs after drug discontinuation similar to those produced by morphine.

The data show that oliceridine is a mu opioid agonist that consistently produces mu opioid agonist behavioral effects in animals. And since, as we all know, mu opioid agonists are drugs of abuse, this meant that it was necessary to conduct a human abuse

potential study with oliceridine in order to provide definitive evidence of whether oliceridine produces rewarding effects in humans.

Human abuse potential studies, HAP studies, evaluate the ability of a test drug to produce positive subjective responses in subjects compared to a known drug of abuse with a similar mechanism of action and to placebo. Subjects in HAP studies are individuals with a history of recreational drug use, but they aren't drug dependent. When the test drug produces consistently large responses on positive subjective scales that are far outside of the acceptable placebo range, it is likely that the test drug has abuse potential.

The HAP study evaluated the abuse potential of a 1-minute intravenous infusion of oliceridine at 1, 2, and 4 milligrams, also morphine at 10 and 20 milligrams, and placebo. This study used a randomized, double-blind, placebo-controlled crossover design in healthy, non-dependent opioid abusers. Intravenous administration, as we all know, produces drug responses that occur immediately after administration but

monitoring for drug responses and adverse events continue throughout the day.

The primary measure that we use in a HAP study is the variable analog scale for drug liking, and this is a bipolar scale of 0 to 100 a hundred where 50 is neutral. So anything below 50 is considered to be drug disliking and anything above 50 is considered to be drug liking.

The positive control drug, morphine, at both doses produced statistically significantly higher mean drug scores of 81 and 89, respectively, compared to placebo, which produced a score of 51, so this validates the study. Oliceridine at all 3 doses produced mean drug liking scores of 71, 83, and 88 that were statistically significantly higher than placebo, which again was in the middle range on drug liking.

We also had them look at some secondary measures, the visual analog scales for overall drug liking, high, good drug effects, and take drug again, and morphine at the 2 doses produced mean scores on each of these positive subjective measures that were statistically significantly greater than placebo.

Oliceridine in all 3 doses tested also produced mean scores on each of these positive subjective measures that were statistically significantly greater than placebo.

We also looked at VAS for bad drug effects and drowsiness, and morphine at both doses and oliceridine at all 3 doses produced mean scores on bad drug effects that were within or close to the acceptable placebo range. Morphine and oliceridine both produced a dose-dependent increase in drowsiness that was outside of the acceptable placebo range for each dose. So these are what we would expect.

In the dose comparisons, as we heard before, there's a 1 to 5 ratio, so the 2-milligram oliceridine dose produced similar responses to the 10-milligram dose of morphine on all positive and negative subjective measures, and similarly the 4-milligram dose did the same compared to the 20-milligram dose of morphine.

During the HAP study, the subjects were also asked does this drug that you're on today feel like another drug. And there are a whole range of drugs

that are asked about, but of interest to us are the ones that are related to opioids. Both oliceridine and morphine were identified as morphine or oxycodone, and the range was very similar, 72 to 84 for oliceridine; 88 to 99 for morphine. They were also identified as codeine and heroin with somewhat less scores. So oliceridine was consistently identified as one of several opioids familiar to drug abusers.

There were adverse events. We look at the abuse rated adverse events in the HAP study, and euphoria was reported at a high rate for both oliceridine and morphine, 38 to 58 percent for oliceridine; 50 to 69 percent for morphine.

Somnolence was also reported at a high rate for both, 8 to 20 from oliceridine and 15 to 33 percent for morphine. Parasthesia was also frequently reported for oliceridine, 3 to 8 percent, and for morphine, 8 to 19 percent, but placebo did not produce any reports of these adverse events.

The conclusions from the HAP study are that oliceridine produces increases on positive subjective measures such as drug liking, overall drug liking,

high, good drug effects, and take drug again that were far outside of the acceptable placebo range. Oliceridine was also identified as an opioid and produced adverse events that included a high rate of euphoric effects.

These drug responses from oliceridine parallel those produced by the positive control drug morphine, so oliceridine produces classic opioid responses in healthy individuals with a history of opioid abuse that are similar to morphine.

Our final conclusions about the abuse potential of oliceridine are that animal and human studies consistently show that oliceridine is a mu opioid agonist with an abuse potential, overdose potential, and ability to produce physical dependence that is similar to other mu opioid agonists such as morphine. So CSS, my group, and the applicant are in agreement, as you heard earlier, that these data show that oliceridine has high abuse potential.

Therefore, it does not appear that biased agonism of oliceridine with regard to preferential recruitment of G-protein over beta arrestin translates

into a human safety advantage for oliceridine compared to traditional mu opioid agonists.

Now I'd like to introduce Dr. Travis, who will speak to us about efficacy.

FDA Presentation - James Travis

DR. TRAVIS: Thank you, Dr. Bonson.

I will now give an overview of my presentation. First, I will discuss the applicant's efficacy analyses and conclusions. I will then present and discuss FDA's efficacy analyses and conclusions. Following the efficacy assessments, I will present the applicant's analyses of the respiratory safety data collected in the phase 3 studies. Finally, I will present quantitative analyses that combine both the efficacy and safety to assess the benefit-risk relationship for oliceridine.

The applicant conducted two efficacy studies, 3001 in patients undergoing bunionectomy, and 3002 in patients undergoing abdominoplasty. The overall design of these studies were similar with a few notable differences, including the duration of the study period, which is 48 hours for 3001 and 24 hours for

3002.

Both studies had the same objectives, first to evaluate the analgesic efficacy and safety of oliceridine in comparison to placebo, and second to test the safety and efficacy of oliceridine in comparison to morphine to establish whether there is a clinically meaningful benefit for oliceridine compared to morphine.

The applicant proposed a novel responded definition with patients classified as responders if they completed the study with an improvement from baseline in some pain intensity differences, or SPID score, of at least 30 percent with no use of protocol-specified rescue medication without early discontinuation of study medication.

They had to meet the study medication dosing limit of 3 PCA syringes or 6 clinician-administered supplemental doses within the first 12 hours. This endpoint is novel, and FDA has concerns with its implementation and interpretability, so we reanalyzed the studies using more standard methods.

The applicant included one safety endpoint,

respiratory safety burden, in the testing hierarchy for both studies. This was a key secondary endpoint and came immediately following the primary efficacy analysis in that testing procedure. The applicant defined the respiratory safety button as the cumulative duration of respiratory safety events, where a respiratory safety event was defined as any clinically relevant worsening of respiratory status determined by the investigator.

Here is the dosing schedule used in both studies. Patients were randomized to 1 of 5 treatment arms: placebo, morphine, or one of 3 oliceridine treatment arms. Patients received an initial loading dose, which was either 1.5 milligrams of oliceridine, 4 milligrams of morphine, or matched placebo. Patients then received demand doses via PCA pump with a 6-minute lockout interval.

The 3 oliceridine treatment arms each received different demand doses with demand doses set at .01, 0.35, or 0.5 milligrams. The morphine treatment arm demand doses were set at 1 milligram. Patients could receive additional clinician-administered supplemental

doses, at most, 1 per hour.

The allowed dose was 0.75 milligrams for oliceridine and 2 milligrams for morphine. Etodolac was included as the only protocol-specified rescue analgesic, but there was also extensive non-protocol specified rescue analgesic use. While the applicant did not consider this as a rescue in their calculation of responder for efficacy, my analyses did.

I will now present the efficacy analysis. The applicant analyzed the response rates using a logistic regression model, which included treatment group as a fixed factor with baseline pain score and study site as covariates. To adjust for multiplicity, the applicant used Hochberg adjustment to control the overall type 1 error. Simply put, if the largest p-value was greater than 0.5, then the next largest p-value was tested at 0.025. If this p-value was not less than 0.025, then the last value was tested at 0.167.

The applicant's original analyses ignored the use of non-protocol specified rescue medication. This is corrected in the analyses that I will present. Here are responder analyses with the non-protocol specified

rescue medication included.

The applicant concluded that all 3 dose regimens of oliceridine demonstrated superior pain relief compared to placebo. Using the applicant's methodology, we see no difference between oliceridine and morphine, and we see only 4 percentage points between the responder rate for morphine and the 0.35- and 0.5-milligram oliceridine treatment groups.

For reasons I will now discuss, we don't believe that this adequately characterized the efficacy of oliceridine compared to either morphine or placebo.

One issue with the response definition is that it truncates the improvements in SPID score to either less than 30 percent or greater than 30 percent, turning a continuous measure into a pass/fail. Patients who experienced a 30 percent reduction are treated exactly the same as patients who experienced much greater pain relief. This causes the difference between oliceridine and morphine to be understated.

The responder definition also treats rescue medication very harshly and may underestimate the treatment or placebo effect in patients that use more

rescue. Rather than use the applicant's responder definition, we reanalyzed the SPID scores using an analysis of covariance model with treatment and site as factors and baseline pain score as a continuous covariate.

To account for rescue use, we carried forward the pre-rescue pain scores for 6 hours following use of rescue medication, except if the observed score exceeds the pre-rescue score. Six hours was the prespecified dosing interval for protocol-specified rescue medication.

Observed scores were used where available after treatment discontinuation. Intermittently missing pain scores were imputed using linear interpolation, and missing data following treatment discontinuation was imputed using the applicant's prespecified methods.

The following figure shows the pain scores over time for all 5 treatment arms using the imputation scheme I just described. The X-axis shows the time since the initial loading dose, and the Y-axis shows the average pain score for each treatment arm at each

time point. Placebo on top clearly does worse than all the other treatment arms.

Morphine shown at the bottom provides the greatest pain relief on average from roughly hour 4 to the end of the study. The oliceridine doses fall in the middle in dose order with the 0.1-milligram dose providing the least pain relief and the 0.5-milligram dose providing the greatest pain relief.

The results from the FDA statistical analyses are shown in this table. The results are consistent with the previous figure, with placebo patients showing the least relief, morphine showing the greatest, with oliceridine falling in the middle in dose order.

All 3 doses of oliceridine provided statistically significantly greater pain relief than placebo. In contrast to the applicant's analyses where there were no differences, there are now statistically significant differences between morphine and the 3 doses of oliceridine in this study.

Our process for 3002 was the same. Again, the applicant concluded statistically significant differences between all 3 dose regimens of oliceridine

compared to placebo and again found response rates within 5 percent of morphine for oliceridine 0.35 milligrams and 0.5 milligrams. This time, however, the odds ratio response for oliceridine 0.1 milligrams and morphine was statistically significant.

Using the same methodology presented for study 3001, we obtained this figure, with the X-axis, again, showing the time since the initial loading dose and the Y-axis showing the average pain intensity at each time point for each study arm.

Morphine, again, clearly provides the greatest pain relief with the oliceridine doses falling in demand-dose order. In this study, patients in the placebo group reported less pain on average for hours 8 through 24 than patients in the 0.1-milligram oliceridine treatment group.

When we compare the SPID scores for oliceridine 0.1 milligrams and placebo, the outcomes are very similar and no longer statistically significantly different. Formal hypothesis testing still found significant differences for the 0.35- and

0.5-milligram doses of oliceridine.

Morphine was superior to the 0.1- and 0.35-milligram oliceridine doses, and though not statistically significant, the SPID scores for the oliceridine 0.5-milligram group were lower than the morphine treatment group.

I will now present the results of the respiratory safety analyses. Respiratory safety events were infrequent even among even among the morphine and highest dose oliceridine treatment arms, where that most about 20 to 30 percent of patients experiencing any events in either study. So the applicant used a nonlinear mixed model with two components to analyze this endpoint.

First, the percentage of patients who experienced respiratory safety events was modeled using Firth logistic regression model. Second, the cumulative duration events for patients who experienced at least one event was modeled using a gamma regression model. The model provided estimates for each component, and then multiplied together to estimate the overall average duration of events among the entire

population.

The objective of this analysis was to evaluate whether there was a clinically meaningful benefit in respiratory safety for oliceridine over morphine. There were several issues with these analyses. First, FDA does not agree with how this endpoint was defined as it is subjectively defined based on the investigator's discretion, which makes it difficult to interpret.

Second, as you will see, there was no clear benefit for oliceridine compared to morphine. And third, since there was a clear dose response in both efficacy and safety, it is especially important to analyze numerical trends in the safety in the context of the observed obsessed efficacy.

To address the final point, following the respiratory safety analyses, I will present additional analyses that simultaneously explore analgesic efficacy and safety.

The results of the applicant's analysis of the respiratory safety burden for the bunionectomy study 3001 are shown in this table. The numbers in the

table represent the cumulative duration in hours of the respiratory safety events.

The observed in the model-estimated cumulative duration of safety events both exhibit a clear dose response relationship for oliceridine. And while the p-value for the 0.1-milligram dose is less than 0.5, it is not considered statistically significant because of the Hochberg adjustment for multiplicity. The model-estimated respiratory safety burden, seen in the third row, was 15 minutes for oliceridine compared to 33 minutes for morphine for a difference of 18 minutes.

For the abdominoplasty study 3002, we again see no statistically significant differences for any oliceridine dose compared to morphine. The oliceridine 0.1-milligram dose was again not significant after adjusting for multiplicity. For this study, the estimated difference in duration of respiratory safety events between oliceridine 0.5 and morphine was about 5 minutes compared to 18 minutes for the previous study.

I will now move on to the quantitative benefit-risk considerations. First, I'll present an

analysis, which combines the efficacy and respiratory safety analyses presented previously. I will then present a comparison of the efficacy and selected adverse event rates. I will only present the results of study 3001, as for study 3002, the difference in duration of respiratory safety events between oliceridine and morphine was much smaller, and the conclusions are clearer.

First, as a reminder, I will present this plot of the relative efficacy observed in the study. The X-axis shows the model-estimated pain intensity differences for each of the treatment arms. The Y-axis shows the different treatment arms. And again, we clearly see that morphine was the most effective in this study, followed by the oliceridine dose groups in descending order with placebo as the least effective.

Moving on to the respiratory safety, here's a plot of the model-estimated duration of respiratory safety events by dose group. The X-axis shows the treatment groups and the Y-axis shows the model-estimated cumulative duration of respiratory safety events in hours. Placebo is omitted because

there weren't any placebo patients who experienced events, and we again see a clear dose response for oliceridine in this analysis.

Combining both the efficacy and respiratory safety plots on the same axis, we get the following plot with model-estimated SPID scores shown on the horizontal axis and the model-estimated cumulative duration of respiratory safety events shown on the vertical access to get a simultaneous view of benefit-risk respiratory safety.

The dose of morphine included was significantly more efficacious than the study doses of oliceridine, and we see a clear separation in the efficacy outcomes. These differences in efficacy make it difficult to interpret the meaningfulness of any change in the respiratory safety.

The objective of this plot is to compare the relative efficacy of oliceridine and morphine versus placebo to the relative rates of adverse events. For this forest plot, points to the left of the zero line represent an improvement relative to placebo. Points to the right represent a decline in comparison to

placebo.

As you have previously seen, all oliceridine treatment arms and morphine demonstrated greater pain relief relative to placebo, which is represented by point estimates and confidence intervals entirely to the left of the zero line.

For the adverse events, we will present point estimates and confidence intervals of the absolute differences in the percentage of patients with any treatment-emergent adverse events and three selected opioid-related adverse events: hypoxia, nausea, and somnolence. With the exception of somnolence, patients receiving morphine experienced significantly more adverse events than patients receiving placebo.

While the highest dose of oliceridine 0.5 milligrams has significantly lower efficacy compared to morphine, opioid-related adverse event rates are similar.

To conclude, there is replicated evidence of efficacy versus placebo for oliceridine in two studies for 2 oliceridine dose regimens, 0.35 and 0.5 milligrams. There was a clear dose-response

relationship for both efficacy and safety for oliceridine. However, the efficacy of oliceridine is lower than the morphine dose selected for study, and this has to be taken into account when assessing the comparative safety. The applicant did not show a respiratory safety advantage for any of the doses of oliceridine compared to morphine.

I will now return the presentation to Dr. Kilgore, who will present a comprehensive safety evaluation and a summary of the benefit-risk considerations.

FDA Presentation - Elizabeth Kilgore

DR. KILGORE: I will now present the agency's safety assessment and benefit-risk considerations for oliceridine. The presentation will include a discussion of dosing in the phase 3 studies, exposure and safety database, the key safety findings, submission-specific safety findings, and benefit-risk considerations.

For dosing, Dr. Travis has described the phase 3 double-blind studies and dosing in those studies. In study 3003, a phase 3 open-label study in surgical and

medical patients, patients also received PRN dosing. The major difference here is the lack of a comparator as well as differences in initial dose and supplemental dosing frequency. Due to PRN dosing, there was a wide range of exposure to oliceridine.

As a result of this PRN dosing, even if a patient was randomized to one dose, the cumulative exposure to study drug varied considerably. This was considered during interpretation of safety data.

Although the agency reviewed the data in a number of ways, our primary safety analysis was the individual phase 3 controlled study by treatment regimen to consider the safety of the dose groups separately, the safety results in the context of the efficacy results for a specific oliceridine dose the key differences between the studies.

For exposure, a total of over 1800 unique individuals received at least one dose of oliceridine. Of these, there were greater than 1500 with moderate to severe acute pain exposed in the phase 2 and phase 3 studies. During the review cycle, the applicant revised the dosing instructions and maximum daily dose

for the label a number of times. Currently, the applicant proposes a maximum daily dose of 40 milligrams and a PCA demand dose of 0.1 and 0.35 milligrams.

This figure is a histogram of the frequency of cumulative exposure to oliceridine for the first 24 hours for the pooled phase 2 and phase 3 studies. The vertical access displays the number of patients and the horizontal axis shows the cumulative exposure in milligrams.

In prior advice, the applicant was advised of a required exposure for at least 350 patients at the highest plan dose. The applicant initially proposed 100 milligrams daily, shown on the far-right arrow, but few patients were exposed. They now propose the 40 milligrams daily, shown on the middle arrow, but exposure still does not meet the required safety database. The highest dose that at least 350 patients were exposed to during the first 24 hours was 27 milligrams of oliceridine shown at the first arrow.

The agency's conclusions regarding the safety database are that the exposure safety database is

smaller than the agency's recommended to evaluate and support the safety of oliceridine for the proposed label. The highest dose with the longest actual duration that had at least 350 patients exposed was 37.2 milligrams, administered over a natural duration of at least 34.5 hours.

This exposure database does not appear adequate to support the proposed labeling that includes a maximum daily dose of 40 milligrams without a limit on the duration of use.

I will now discuss the key safety findings. There were no deaths in clinical development. The following key safety events will be discussed. Serious adverse events, discontinuations due to adverse events, common adverse events, and submission-specific safety considerations. For SAEs, discontinuations due to AEs, and common AEs, I will review the data for the controlled phase 3 studies followed by study 3003.

Serious adverse events. This table show serious adverse events by randomized treatment group stratified by study. I will use similar tables to display other adverse events in this presentation.

In study 3001, there were no SAEs as shown highlighted. In study 3002, the occurrence of SAEs appeared dose dependent for oliceridine treatment as shown in the highlighted row. In study 3002, the percentage of patients with SAEs was higher in the oliceridine 0.35-milligram group and the 0.5-milligram group compared to the morphine group.

SAE preferred terms in oliceridine treated patients included one case each of post-procedural hemorrhage, syncope, lethargy, abdominal wall hematoma, and deep vein thrombosis. In study 3003, 26 patients, approximately 3 percent, experienced a total of 32 SAEs. The types of SAEs fell into three broad clinical categories: post-operative, other, an opioid related.

I will now discuss adverse events leading to discontinuation. This table shows adverse events leading to discontinuation stratified by study. As seen in the table, the percentage of patients in the oliceridine treatment arms who experienced discontinuations due to adverse events in the controlled phase 3 studies appeared generally dose dependent.

The percentage of discontinuations due to adverse events was higher for oliceridine 0.35 milligrams and 0.5 milligrams compared to morphine in study 3002. There were no adverse events leading to discontinuation in the placebo or oliceridine 0.1-milligram treatment groups. As shown, the types of adverse events leading to discontinuation in oliceridine were primarily opioid related.

Notably, patients in the oliceridine and morphine treatment arms discontinued due to oxygen saturation decreased and hypoxia. In study 3002, more patients in the oliceridine arms than the morphine arm discontinued due to hypoxia. Thus, there was not a consistent trend toward improved respiratory safety for oliceridine compared to morphine based on adverse events leading to discontinuation.

In open-label study 3003, a total of 17 patients, approximately 2 percent, experienced 29 treatment-emergent adverse events leading to discontinuation. As with SAEss, the types of preferred terms leading to discontinuation in study 3003 were across a wide range of clinical categories.

Common AEs. This table shows common adverse events stratified by study. In studies 3001 and 3002, the percentage of patients who experienced the most common adverse events was dose dependent for the oliceridine arms. The percentage of patients with common adverse events for the oliceridine 0.5-milligram arm was similar to that of morphine.

Nausea and vomiting were the two most frequently occurring adverse events in the oliceridine and morphine treatment groups. As highlighted on this slide, the oliceridine 0.5-milligram had similar incidence of nausea to that of morphine in both studies. In contrast, the percentage of patients with vomiting was lower for oliceridine 0.5-milligrams versus morphine in both studies.

The agency's conclusions regarding the SAEs, AEs leading to discontinuation, and common AEs show that oliceridine adverse events were generally dose dependent. The types of common treatment-emergent adverse events were primarily opioid related in oliceridine and morphine treated groups.

Next, I will discuss specific safety

considerations for hepatic safety, respiratory safety, and QT prolongation.

Hepatic safety. In the phase 3 controlled studies, generally the frequency of occurrence of elevated transaminases between oliceridine and morphine treatment groups was balanced or slightly higher in oliceridine compared to morphine at some dose strengths.

As highlighted, in study 3002, transaminases greater than 20 times the upper limit of normal occurred only in the oliceridine treatment group. As shown in this table, for pooled all phase 2 and phase 3 studies, there was a higher percentage of patients in the oliceridine treatment group who experienced greater than or equal to 20 times the upper limit of normal transaminases compared to no cases in the placebo or morphine groups.

These three cases represent agency-identified select cases of interest. The first two cases are patients who experienced transaminase elevations and concurrent total bilirubin elevation. The third case is a patient who experienced a serious adverse hepatic

event with markedly elevated transaminase levels.

The agency found that all 3 cases were confounded. However, we brought them before the AC to point out that although the cases were confounded, such events did not occur in the placebo or morphine treated groups across studies.

The agency's conclusions regarding hepatic safety are that there was a higher percentage of patients in the oliceridine group who experienced greater than or equal to 20 times upper limit of normal transaminases compared to no cases in the placebo or morphine groups.

There were 2 cases with transaminases greater than or equal to 3 times the upper limit of normal with concurrent total bilirubin greater than or equal to 2 times the upper limit of normal, and an SAE of hepatic failure. The cases appeared confounded.

The three cases of interest all occurred in study 3003, which was open label without a comparator group, limiting conclusions. Study 3003 was designed to represent a real-world population of patients that may receive general anesthesia and multiple concomitant

medications.

Respiratory Safety. Dr. Travis has discussed respiratory safety as related to efficacy. I will present the agency's findings of select respiratory parameters. Respiratory safety was analyzed by the agency in a number of ways. The agency did not agree with the applicant's primary respiratory safety endpoint as discussed by Dr. Travis.

This table shows the clinical respiratory parameters of interest that included oxygen saturation less than 90 percent; treatment-emergent adverse events; in the respiratory, thoracic and mediastinal disorders system organ class; and a number of patients with any O2 administration required.

Both studies showed dose-response relationships between increasing oliceridine dose in all three of the parameters of interest shown. In both studies, treatment-emergent adverse events were slightly higher in the oliceridine arm compared to morphine, as highlighted in the table.

The agency's conclusions regarding respiratory safety are that in studies 3001 and 3002, there were

dose-response relationships between increasing oliceridine dose and select respiratory parameters. While there were trends showing a decreased percentage of respiratory events, as defined by the applicant, with oliceridine than morphine for some parameters, this was not consistent across all parameters.

The agency has determined that there is not sufficient data to support a conclusion that oliceridine has a respiratory safety advantage relative to morphine under the conditions studied.

I will now move to the QT prolongation. The purpose of the thorough QT study is to assess the effect of the drug on the QTc interval at doses that cover the high-drug exposure scenario in patients. Predicting the QT risk in patients depends on understanding the exposure-response relationship and mechanism.

The applicant's thorough QT study assessed the effect of oliceridine on the QTc interval at 3 and 6 milligrams. Results showed a dose-proportional increase in QTc at approximately 1 hour after time of peak plasma concentration. There are a number of

limitations of the QT study as noted. Primarily, the study did not identify the mechanism of the delay, and the study did not assess exposure at the therapeutic dosing regimen.

The agency did provide advice to the applicant after the through QT findings to conduct safety ECG monitoring at defined intervals. Upon review of the NDA, the agency determined that the frequency of ECG assessments in the phase 3 studies was too limited to inform regarding the potential QT risk.

The agency's conclusions for QT prolongation are that the thorough QT study showed that single doses of oliceridine prolong the QTcF in a dose-dependent manner with a delayed onset. The proposed mechanism for the delayed onset of the QTcF prolongation remains unclear. The agency has determined that the submitted data are not adequate to evaluate the QT effects of oliceridine.

Lastly, I will discuss benefit-risk considerations. As patients were randomized to 1 of 3 oliceridine doses and took the study medications as needed, there is complexity in the evaluation of the

relationship between oliceridine dose and safety efficacy outcomes. The agency focused on analyses by randomized treatment group in the individual studies to have a clinically relevant understanding of the safety and efficacy data by oliceridine dose.

When considering the benefit-risk of oliceridine compared to placebo and the active comparator morphine, the agency determined that when compared to placebo, oliceridine demonstrated statistically significantly greater reduction in pain. In general, adverse events were dose related and consistent with an opioid safety profile.

When compared to morphine, the oliceridine doses that had fewer adverse events than morphine also were less effective than morphine. There does not appear to be data to support a conclusion that oliceridine has a safety advantage compared to morphine under the conditions studied. Thank you.

Clarifying Questions

DR. ZACHAROFF: Thank you very much, and we will now have time to ask clarifying questions to the FDA presentations we've just seen. Dr. Higgins?

DR. HIGGINS: This question is for Dr. Bonson with regards to the HAP study. I'm struck by the fact that the morphine dosage used for that study is significantly higher than the 4 milligrams used in the trials that we're reviewing today. Can you comment on that difference, that striking different?

DR. BONSON: I can't comment on why they -- we know why they chose the doses that they did for the HAP study, but I don't think that's the question you're asking, is it?

DR. HIGGINS: No.

DR. ZACHAROFF: Dr. McCann?

DR. McCANN: This is about slide 10. You mentioned that we needed 350 patients. What's the magic about 350 patients?

DR. HERTZ: This is Sharon Hertz. The magic is we have to come up with a target number, and in general, we have settled around there. In a setting like this, where we're not even sure what the dosing range will be, we have to pick some number for the maximum dose to see if we can get some trends out of the evaluation of safety by dose. It's really not

scientific.

DR. McCANN: Could I have another follow-up question? Do you have the sponsor submit a data analysis plan before they look at the data?

DR. HERTZ: For the efficacy studies, they are required. They do send in a statistical analysis plan. Is that what you're referring to?

DR. McCANN: Yes.

DR. HERTZ: Yes, and we do look at it. And we do provide comments if we disagree, but it's very difficult to require a change, so sometimes we just have to re-do it ourselves.

DR. McCANN: Because it seems like you had fundamental differences between what the outcome measures should be.

DR. HERTZ: Right. Here's just a couple of points that might help clarify some of that. For efficacy with an analgesic, we require a demonstration of superiority to a comparator, not necessarily placebo. But noninferiority studies are very hard to interpret in analgesia because you could have two ineffective doses that look the same, two good doses

that look the same, so the most common comparator is placebo.

When we have multiple comparisons, multiple endpoints, we do ask for that analysis to all be prespecified depending on the importance of the different comparisons. So for instance, sometimes sponsors will identify the target dose that they think is going to be the right one that will perhaps be first in a step-down procedure, different attempts to preserve alpha. If there are secondary endpoints that they want to have a statistical comparison for, that will also be taken into consideration.

So yes, that's all done in advance. And our team looks at it. But when we disagree, if the study is designed so that it can meet its objectives, even if we don't agree in how the data are analyzed, we don't interfere with the study proceeding. We don't have any other way to force compliance with a particular analysis. And when somebody wants to evaluate novel endpoints, that's fine, but we want to understand what the relevance is for that.

For instance, we know from some work in

different settings, for instance some of the work by John Farrar, that a 30 percent reduction in pain or -- I forget the exact number on the numerical rating scale -- difference in pain may be clinically relevant to a patient. We don't know what that number is for some pain intensity difference because the manner in which an area under the curve type of analysis is designed will affect what the numbers are, what the numbers reflect.

It's very hard to conceptualize the details of a specific SPID when you're looking at a number. Maybe Abby can visualize it, but perhaps not the rest of us. So with a responder definition, there's a dichotomy, but it can be very clear if the dichotomy is based on well-known, recognized criteria.

So we were not able to agree that the chosen responder definition had all of the elements properly supported, and that's why we went ahead and did something else.

DR. ZACHAROFF: Dr. Litman?

DR. LITMAN: Thank you. Ron Litman. Mary Ellen, in answer, I also looked at the 350, and I was

wondering what that was. And I just assumed -- I went back to the old Lippman-Hand article from JAMA in the '80s, and the rule is basically that if no events occur, you divide by 3 and you have a 95 -- Abby, you can help me with this, a 95 percent probability that it will be less than 1 percent, about. 350 divided by 3 is sort of around 1 percent.

The question I had, though, is something more. There seems to be this elephant in the room here that we haven't talked about yet. And that is there's quite a difference in interpretation of the data between the FDA and the sponsor. So it seems to me to be that difference -- at the heart of that difference is how you interpret efficacy.

So I would just would like more maybe clarification from the FDA as to what that -- how do we interpret efficacy? When we look at the FDA's data, clearly their doses of oliceridine were not as effective as morphine. And that can completely explain why their side effects were less. You can't compare doses that are not equipotent, but yet the sponsor seems to think that those are not realistic clinical

outcomes.

DR. MAYNARD: This is Janet Maynard from the FDA. I think we totally agree with you that we thought it was very important to consider both safety and efficacy when we were thinking about the results from the trial. And we tried very hard to show the results, thinking about those different parameters, especially considering that this medication would be used in a setting where it would be titrated to effect.

So we felt it was very important in that setting to understand both efficacy and safety when comparing those issues.

DR. ZACHAROFF: Dr. Solga?

DR. SOLGA: This question is for Dr. Kilgore or if feasible, Dr. Watkins. I need some help again. I seem to be the only person in disagreement about one of the case vignettes about liver safety. Case 3 on slide 41 was described in page 81 of the FDA briefing document. It describes a 55-year-old man with knee arthroplasty who went home after a painful operation and then reappeared to the emergency room several days later with a chief complaint of abdominal symptoms; was

found to have a strikingly elevated AST, massive centrilobular necrosis on liver biopsy, and renal failure.

Certainly as discussed, ischemia is in the differential diagnosis of pain; "increase in transaminases is quick, high, fast, strong." Of course, so is acetominophen. In this instance, I wondered why that wasn't at least considered in the differential diagnosis.

Dr. Litman had asked Dr. Watkins earlier are there any possible explanations, biologically, why a study drugs seems to have a minor increase but apparently a real increase in hepatic safety signal compared to placebo or morphine. I speculate that surreptitious [indiscernible] or prescribed to acetaminophen use could be one of them if patients didn't feel like their pain was adequately controlled.

DR. MAYNARD So if we could have slide 41, please, from Dr. Kilgore's presentation. So this is the slide you're referring to, and you're referring --

DR. SOLGA: Yes, it's in page 81 of the briefing document in much greater detail.

DR. SOLGA:

DR. MAYNARD Right. And your specific question was did we consider whether or not acetaminophen [indiscernible] --

(Crosstalk.)

DR. SOLGA: Yes. The explanation in both, the FDA briefing document -- and if this is the same case as Dr. Watkins brought up earlier -- was this was ischemia and/or bad humerus from whatever happened in the OR, and a residual effect. I just don't understand why this isn't simply acetominophen.

DR. HERTZ: I don't think we had the details of all of what that patient may have been exposed to, particularly after discharge. So I think that's the problem. When we try to ascribe causality between what we're seeing in safety and the study drug, it's very difficult. We noted these, but it was suspicious. That's as far as we can take it in this context.

DR. KILGORE: And just to add to that -- this is Dr. Kilgore -- we did say that the cases were confounded. That's what we mean. It could be any number of medications that were contributing to this

picture. Certainly, one of them could be APAP. But then you run into the risk of saying, well, it could be APAP, but it could also be the study drug. So that's one of the issues that we have to consider.

DR. SOLGA: I acknowledge the difficulties in teasing these apart, especially when folks are discharged from the hospital. But when it comes to confounders, really, acetaminophen is unique in its potential to dramatically increase AST and ALT so quickly. There's almost no other drug that can do that. And it is an analgesic medication. Therefore, it is a specific confounder that bears directly on the study drug in question.

DR. ZACHAROFF: Dr. Terman?

DR. TERMAN: Thank you. I'm also interested in the human abuse potential study and just want to make sure that I understand. In the FDA's review, the data, as I read it, too, is that there's less abuse or equal potential compared to morphine.

DR. BONSON: Equal.

DR. TERMAN: So less or equal, not more. So when I hear about a fast-acting IV medication, I worry

about there being a chance of it being more. But as you look at the data, there's no evidence for that. It's not a ceiling effect.

DR. BONSON: For more, correct. But these are at the doses tested.

DR. TERMAN: Right, but the dose at least based on some of the early pain dosing was pretty effective when you gave it in a big dose like this.

The other question I have is also about the 350. This must come up a lot because if a drug is really effective, for instance, you might not need huge doses. My suspicion is if you want big doses, all you have to do is put it out there and remove the elimination of opioid-tolerant patients, and you'll get big doses.

How do you figure out, before you put it out there, what huge doses might do? Because it might be difficult to get 350 in a efficacious compound.

DR. HERTZ: This is Dr. Hertz. We don't know everything about a new drug, especially a novel drug like this when it gets approved. If we held out until we could gather a lot more information, we would

potentially be limiting the availability of products that have the potential for providing a benefit.

So at some point in time, we have to say this looks reasonable. We have to hope that with a new product, prescribers will pay attention to the label, and we have to label very clearly what we know about it. And then if there is interest in extending the dosing range in the labeling, we would require additional studies with more data to do so.

I don't know if that's a satisfactory answer, but at some point, you just have to say meet this mark and let's see what you've found. Had there been something unexpected in the dosing range studied, we might ask for additional information or limit the dosing lower. As it was, the proposed dosing from the company initially did not turn out to be what was used in the clinical studies, so we worked to reduce what might occur in labeling to at least have some data on that high range, that high end of the range.

DR. TERMAN: Thank you.

DR. ZACHAROFF: Mr. O'Brien?

MR. O'BRIEN: Thank you. My question is for

Dr. Kilgore. It's a general question, I guess. Early in the presentation, Dr. Bonson had indicated it is clear evidence that in fact oliceridine is a biased agonist. And along with that, the hypothesis is, it could therefore give a drug that is the same analgesic effect but safer for the patient. However, the conclusion from the FDA is in fact that it doesn't show that for this particular drug.

My question is, are you questioning the hypothesis or is it just the methodology and the data that you have?

DR. KILGORE: Well, from my perspective, I'm just reporting the results. We just reported what we saw.

I'll let Dr. Hertz address it.

DR. HERTZ: It's very difficult to try and determine what the relative respiratory depressant effects are in a clinical setting, particularly when you're dealing with an analgesic that's titratable. And if you don't allow titration of an opioid analgesic, it is very hard to have a good understanding of the balance of efficacy and benefit because you may

impose a dose that's too low, that looks safe but doesn't work, or you may impose a dose that's too high and everybody's too sleepy,. I'm sure they may not be complaining of pain, but it's not where you want to go.

So what we're disagreeing with at this point is that the data collected are the correct data for understanding whether or not there's a signal. We have seen some other attempts to evaluate this that have looked at much more standardized and much more closely monitored respiratory status, but it's very difficult to do. You can't deny the experimental models. The question is how does that transition, or translate rather, into the actual clinical setting. And right now, that's why we're still struggling with that balance between benefit and risk.

Now, in some settings, you can sort of push the population to have the adverse event more. You look at a high-risk population. You push. For instance, in studies with post-op nausea and vomiting, you can enrich for people who have a history of responding in that manner to opioids. And then you get a higher background rate, and you can differentiate the

drugs better. But I'm not sure how many IRBs are going to let us push an opioid to respiratory depression in a post-op setting; rightfully, they shouldn't.

So it's very hard to get -- if you look at the background rate for significant respiratory depression in this context, it's fairly low. Depending on the articles, there's a different range, bit it's very hard to get enough information to clearly identify that differentiation. And then, as you've heard, we're struggling with trying to figure out how to define what's a comparable level of efficacy.

So I think the short answer, now that the long answer is done, is we're not saying it's not possible. We're just saying we don't yet have evidence to support -- in our minds, we didn't see evidence to support that it was in place in this setting.

DR. ZACHAROFF: Okay. With that, we're going to adjourn for lunch. We will reconvene again in this room in one hour at 1:00 PM. Please be advised to take any personal belongings you may have with you or you want at this time.

Just for the sake of saying this again,

committee members, please remember that there should be no discussion of the meeting during lunch among yourselves, or the press, or with any other member of the audience. Thank you. See you back here at 1:00.

(Whereupon, at 12:01 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. ZACHAROFF: Okay. We will formally reconvene. Welcome back, and shortly, we will begin our public hearing session.

Both the Food and Drug Administration and the public believe in a transparent process for gathering the information and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that is important to understand the context of the 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 this meeting. Likewise, FDA encourages you at the

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues set before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today for this open public hearing session is for it 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 only, when recognized by me, approach the podium and speak. Thank you for your cooperation.

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

DR. ANSWINE: My name is Dr. Joseph Answine, MD -- I prefer to be called Joe -- representing myself. As for any declaration, I've been an advisor in the past for Trevena, but I am not being paid for this presentation.

I want to thank you for the opportunity to speak in front of you in favor of oliceridine and describe to you the difficulties we face as anesthesiologists today. I'm a full-time practicing anesthesiologist in an academic as well as a private setting, and I personally care for thousands of patients yearly. The difficulties lie in the fact that we are trying to move many patients through the perioperative process. However, our patient population, due to age and illnesses, is become exceptionally challenging with increase in obesity, obstructive sleep apnea, diabetes, cardiac disease, and pulmonary abnormalities such as COPD.

Our task to provide a safe outcome is becoming far from easy, and one of the biggest challenges we face for major surgeries is opioid-induced post-operative complications, especially involving the

respiratory system. Combined opioid-induced respiratory depression with obesity, obstructive sleep apnea, and cardiac disease, and the possibility of major post-operative morbidity increases dramatically.

One of my special patient populations is the extremely obese individuals having gastric sleeve bariatric surgery prior to having cardiac surgery. They are actually deemed too sick to have cardiac surgery based on their extreme weight. My goal is to get these extremely ill patients through the bariatric surgery so that months down the road, they're well enough to have their heart fixed.

Imagine the challenge that I face with this patient population. Every potential complication is not academic anymore but highly likely during the perioperative process, and even minor complications such as minimal respiratory depression after extubation is given very little margin for recovery, especially with underlying pulmonary hypertension, which is quite common due to the cardiac disease and obstructive sleep apnea.

With the addition of medications with

selective G-protein coupled opioid receptor activation, we are improving our chances of significantly reducing post-operative comorbidities and our very sick patients.

Oliceridine's effectiveness at treating acute perioperative pain, having no obvious active metabolites, having a rapid onset, and demonstrating a trend towards less respiratory depression, gives us an opportunity to reduce the risks of our pain management regimen. Again, its acceptance and availability is vitally important to our pain management regimen, as well as the future development of medications of this type.

In my quest for the utilization of multimodal pain management, I've learned that opioid avoidance is impossible in most cases for post-operative pain, but opioid minimization is possible. However, we should still continue to strive for a better opioid, one that has less of a dramatic effect on the patient's passage through the post-operative process.

Although we have yet to find the perfect acute pain medication, we are making steps forward. I do

think that oliceridine is the next important step towards that goal. Again, committee members, thank you for your time, and thank you for allowing me to present.

DR. ZACHAROFF: Thank you very much. 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. GRIFFITH: Hello. My name is Suzanne Griffith. I'm a registered nurse who was one of two study coordinators for our site. Prior to that, I worked on post-op floor at Mississippi Baptist Medical Center. I am here at Trevena's request to convey to you how much I believe in this medication and from what I observed as a research nurse who administered it to over 80 patients.

Our patients arrive in recovery in various states of consciousness and pain. We assess their pain level on a scale of 0 to 10. If they were a 4 or above, we dose with oliceridine. Using our nursing judgment exactly as a staff nurse would if they were giving morphine or dilaudid, we gave the patient 1 or 2

or 3 milligrams of oliceridine. Most patients seemed to have immediate relief and were quickly calmed.

I've been doing clinical trials for almost 20 years. When I start a new study, I am sometimes met with skepticism from the hospital staff as to whether or not the study drug will help patients. After we had been working with oliceridine for a couple of months, we had won over the staff.

The recovery nurses were happy to find out they were receiving the study patient actually. And here's why. They didn't have to frequently administer pain medications to fresh post-op patients. They could chart or catch up on charting or even take a break. They knew that with one of the study nurses assessing pain and administering oliceridine, they didn't have to worry about the responsibility of managing the patient's pain.

Here's the key. It wasn't that someone else was doing their job. It was because over those months, those first months, they began to realize how well this drug worked. They had observed how quiet, calm, and restful the study patients were. Pain scores upon

reassessment were down. Oliceridine had won their confidence, and this is a tough group. This is a critical care unit, and the patient must be stable, which includes pain control, before the patient can be taken to a room.

Now to the nursing units. During the handoff from the recovery nurse, one or both coordinators were always present. We reinforced the PCA pain management and study participation education with the family, the patient, and the nurses on the floor.

We made clear to the patient that rescue doses were available as needed. We also stressed if the PCA, which contained the oliceridine, and breakthrough doses of oliceridine were not controlling their pain to please let us know, and they would be switched to a different medication, either morphine or dilaudid. We only had 2 patients out of our 80 who elected to stop oliceridine.

For the floor nurses, the same experiences in recovery, skepticism at first, but then they were very happy to have study patients because they reported they definitely made less trips to the study patients' rooms

to provide breakthrough medication. These nurses spend roughly 25 percent of their time delivering pain medications, so having less calls for extra pain meds helps the nurses address other critical needs.

Now, patient perspective as we observed it. Whenever the other coordinator went in to assess the patient, we found our patients awake, alert, talking to their family members, happily eating a meal, or even walking the halls. We noted less nausea, less itching, and very importantly, quicker return of bowel function.

I know this study was not about that, but I have done so many post-op ileus studies that bowel function seems to work its way into the conversation every time when you're talking to a post-op patient. Also, the patients are told that they can go home once they've had that first post-op bowel movement, so it's like on alert, everyone's radar, and people don't really mind talking about it in the hospital.

There were other things the patients stated such as, "I can press the button, and my pain goes away. And I can talk to my family. And I make sense." They weren't fuzzy headed in other words. "I'm so

happy that I don't have to ask for nausea medication. I always get nauseated after surgery. I'm not seeing spiders on the wall." That was a big one. "Every other time I've had anesthesia, I had to be placed in ICU afterwards. Not this time."

One daughter said she felt this medicine made a huge difference in her mother's recovery, and she was very happy it was available to her. A patient stated she didn't realize how great this medication was until she started taking Percosets, which of course is what she transitioned to, to take by mouth after IV medication was no longer needed. In general, we saw pain relief without the high. And again, this is an observation.

I would like to thank Trevena for writing a great protocol in conducting this trial. With the exception of offering oliceridine instead of dilaudid or morphine in the PCA, we did not change one thing we did for the patients. It was completely standard of care. The physicians love that part, and the patients were much more comfortable participating in the trial. I think if you're trying to prove something is better,

you don't change the fields you're already playing on. You put your drug up against what has been done for years, meaning the standard of care, and see how it performs.

Finally, on a personal note, I would really like to see this drug on the market. I've had a serious reaction to dilaudid. Morphine gives me nausea, vomiting, and itching. I'm running out of options if I have to be hospitalized again. And I strongly believe in this medication for pain. Less side effects, and if available, it would definitely be my choice.

DR. ZACHAROFF: Thank you. 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.

MR. LAPIDUS: Good afternoon. It is my pleasure to be speaking before this FDA committee concerning the efficacy of the drug oliceridine and what my experience was as a patient. My name is Robert Lapidus, and I just turned 70 years old, and I am from San Jose, California. I want to let you know that

Trevena has supported my travel expenses but is not compensating me for my time.

On a personal note, I just wanted to say it's a pleasure to be back in the Washington, DC area. I'm a retired federal employee. I had a great career working for the Department of Defense, Department of Labor, and then I retired and went to become a contractor consultant. I wound up working -- I might even have some graduates here -- at the Federal Executive Institute as a facilitator in Charlottesville, Virginia, and had the privilege of teaching at the key executive program at American University. So it's great to be back home. Sorry we didn't get a Washington Nationals pennant this year.

My wife and I have traveled from California to share my story because it's important for this committee to understand why there is a need for this product. In April of 2017, I was diagnosed with a painful obstruction on my small bowel that necessitated surgery, April 2017 at Good Samaritan Hospital in San Jose.

As a patient in the hospital, I was approached

by a pain management doctor named my Maia Chakerian, who informed me that there was a new experimental drug called oliceridine that was part of a clinical trial to help patients with acute pain. She explained that standard opioid treatment would reduce pain but may slow down bowel movement, which was critically important for restoring me to my health.

My surgeon agreed that this was frequently a problem with standard opioid treatment. Both doctors hoped that this new drug may lessen pain without the negative consequences of slowing down bowel function. Dr. Chakerian did a thorough job of explaining to me the parameters of the study and what my rights were as a patient. I agreed to participate in the study and was receptive to trying this new drug.

I am pleased to report that my pain level was managed very well and that my restoration of bowel functioning was significantly better than that compared to a previous colon surgery I had undergone many years earlier when I had taken standard pain medication.

To administer the oliceridine, a small tube and IV line was inserted in my vein. I was able to

access the medication by pressing a button that controlled when the medicine was injected in order to ease my pain. I felt more in control of managing my own threshold of pain, and oliceridine provided significant relief to me over a period of 2 to 3 days.

On the fourth day in the hospital, the drug was withdrawn and my abdominal pain had dissipated considerably. I was in place on clear liquids and oral Tylenol only. On the sixth day, my normal bowel functioning returned, and I was released on May 5th, which was day 7. This one was at least one week better than my previous surgery, and there was much less of a struggle to resume normal bowel functioning.

My surgeon was pleased with the outcome and felt I had very good progress. In summary, I had a very positive experience with the drug oliceridine, which was very helpful to me in easing my pain level and accelerating me back to full body functioning.

Many thanks for listening to my account. Thank you.

DR. ZACHAROFF: Thank you. Will speaker number 4 please step up to the podium and introduce

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

MS. QUINN: My name is Tina Quinn. I am here from Madison, Mississippi, a suburb of Jackson, and Trevena supported my travel but not my time. I traveled from Mississippi to share my story because I believe it's important for the committee to understand why there is a need for this product.

Let me begin by saying I will celebrate another year of life on the 28th and turn 35 years old. At 32 years old, I was diagnosed with stage 4 metastatic breast cancer while still breastfeeding my 6-month old and third child, only son. My treatment plan was very aggressive with the use of opioids as part of my daily routine for multiple surgeries including a double mastectomy, a liver procedure, reconstructive, IV chemo, and my overall management.

When I was approached regarding this trial, I was having and preparing for my double mastectomy. I wasn't nervous about losing my breasts as I had other concerns, considering this was not my first surgery. My first surgical experience had been an emergency

Caesarean section for a prolapse cord with my firstborn about 12 years prior while stationed in South Korea as an active duty army service member.

The circumstances surrounding the procedure surely were traumatic indeed, but nothing could have prepared me for the pain from having my abdominal cut, stapled, stitched, and glued back together again. This would be my first memorable encounter with opioids.

I remember it hurt to cough, cry, laugh, and any sudden move. I didn't even want to go to the restroom. The pain was unbearable. I remember being administered Percocet 5's and that not being enough, and asking for something more. I remember them giving me ibuprofen for breakthrough pain.

I recall watching the clock every 4 hours because I was so afraid of the pain returning that I didn't want to feel it again, causing further anxiety and distress. I was so afraid I wouldn't receive adequate relief. I had other unwanted side effects, including nausea, sleeplessness, and constipation, as at that time I really wanted to focus on my new sick baby. I battled the constipation and conspired plans

on pushing, sneezing, coughing, and any other effort to attempt to relieve myself.

It would be against that history I would be comparing and preparing myself for my double mastectomy. I was introduced and told about oliceridine, and I was skeptical. I honestly came prepared with my daily opioids to the hospital. I didn't think that oliceridine would be strong enough or could work without the side effects. Considering my diagnosis and reason for my surgery every moment of every day with my family and loved ones was vital.

Well, to my surprise, my pain was totally and completely relieved. I did not require any breakthrough medicine. I did not have an itch to scratch. I remember being completely at ease and not having to ride the PCA pump. I remember not watching the clock, and I definitely remember no constipation. I did not feel as though I was becoming addicted either. My only other concern was when would it be available for consumer consumption and available orally.

I hope in sharing my story today that concern

is unfounded. Please remember me as you consider your decision and vote for approval for this option. Thank you.

DR. ZACHAROFF: Thank you. Will speaker number 5 please step up to the podium and introduce yourself? Please state your name and any organization you're representing for the purposes of the record.

DR. BEARD: Thank you. My name is Tim Beard. I'm a general surgeon from Oregon. I'm in private practice. I do have a clinical appointment at Oregon Health Sciences University, but I just teach medical students. I'm definitely a private practice person and do a high volume of surgery.

I serve as the chair of the Department of Surgery at our group. I've worked in an advisory capacity for Trevena. I'm also the medical director of research at our group. My main interests are enhanced recovery programs after surgery and also post-operative ileus.

I want to talk about three points where this drug I think might be helpful. I think one thing to realize is that in private practice, I don't have

residents, I don't have fellows. I'm the one getting the calls at 2:00 a.m. if someone's nauseated, or someone needs a sleeping pill, or whatever. So it makes a big difference to me and my lifestyle and how my patients do. We try very hard to maximize everything possible in our patients so they can do the best after surgery as possible.

One of the things that wasn't necessarily studied with this drug, but I'm hoping it will have advantages is what was just talked about in post-operative ileus. I do a lot of colon cancer surgeries, and the Achilles heel of that surgery is when people are going to get their bowel function back.

We currently use a drug now, alvimopan, which counteracts opioids. It blocks mu receptors peripherally on the gut because, as you know, opioids prolong ileus in all patients. So we're currently using a drug to counteract the side effects of opioids, but I'm hoping with further studies on oliceridine, that maybe we wouldn't need to do that.

The second area that I think would be important is what I call polypharmacy. I've been here

all morning, and it's very interesting. And as an aside, I think every medical student should have to come to one of these because this is my first one, and I'm impressed with the diligence that's done on these drugs.

When we give pain medicines post-operatively, we now do a very aggressive multimodal pain management, so our patients are getting IV Tylenol. They're getting Toradol. They're getting gabapentin; they're getting Neurontin.

We of course give opioids. You have to give some opioids. But then we're giving a slew of drugs to counteract the side effects of the opioid, so we're giving Zofran, Phenergan, decadron for the nausea and vomiting. We're giving alvimopan, and Miralax for the post-operative ileus. And even though there's a lot of brain power in this room, I don't think anyone knows the pharmacokinetics of all those drugs together.

This is what happens. I get the 80 year old with the colon cancer. I give him this cocktail of drugs, many of which are to avoid opioids. The other drugs I give are to counteract the side effects of

opioids. I'm hoping with a drug that's maybe a little bit cleaner for the mu receptor and the G-synthesis pathway, that we could stop some of this polypharmacy that's going on.

The last point I want to talk about is opioid-related adverse drug events. I'm sure most of you have seen the article in JAMA in May by Sheefi [ph] and others that looked at a large database of this, over 140,000 patients they looked at retrospectively. Over 13,000 had opioid-related adverse drug events, over 10 percent. When patients had these events, they increased their hospital length of stay, increased the cost, increased the chance they had to be admitted to a SNF, maybe a subacute nursing facility postop, and increased the readmission rate.

So any of these complications are difficult. I'm in a private hospital of about 250 beds. At least once a month, probably way more, we have to call a code or a near code for someone that has to be given Narcan. So even though I heard this morning some people say, well, the incidence of these respiratory depression, things are low, if it's your patient, it's a hundred

percent. If it's your family member, it's a hundred percent. And certainly I think there's opportunity where we could do better.

So in closing, I'd just like to read the conclusion of this paper that was in JAMA. It says, "Opioid related adverse drug events are common among patients undergoing hospital-based invasive procedures and were associated with significantly worse clinical and cost outcomes. Hospital-acquired harm from opioid-related adverse drug events in a surgical patient population is an important opportunity for health systems to improve patient safety and reduce costs." And thanks again for your time.

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

MS. THORNTON: Thank you. Hello. My name is Julie Thornton. I am 43 years old, and Trevena has asked if I would be willing to come to speak to you about a drug trial I participated in October of 2016. I come to you from Columbus, Ohio to tell my story.

Trevena paid my travel expenses but is not providing any additional compensation in exchange for my testimony.

I am hopeful for a better way to treat pain with less risk of addiction, which is why I am more than happy to share my experience. On October 4, 2016, I was admitted to Ohio State University Hospital for a total hysterectomy. During my intake process, I was approached by a staff member who asked if I would be interested in volunteering for a drug trial.

I was given a printout of information about the medication and told that this was designed to provide more effective, longer lasting pain relief with less risk of addiction. I was told I would be given my first dose of the medication after surgery while still sedated, and I believe one or possibly two more doses as needed while I was still in the hospital. I agreed to participate.

My surgery went as planned, and the medication was given to me before I awoke. When I came out of anesthesia and my grogginess wore off, I felt fine. I was wheeled back to my recovery room, and I did not

need any assistance transferring from one bed to the other.

Less than an hour later when a nurse came to check on me, I asked if I could get up and walk around. She wanted me to rest more and thought it was not a good idea to stand and walk so soon after the surgery So after another hour or two, she agreed to let me walk a short distance with her next to me to make sure I didn't have any trouble or to fall.

When she realized I did not need any support, she walked with me allowing me to go farther and see how I was doing. We walked down the hall and around the floor. After that, she allowed me to get up and walk around as I pleased so long as I didn't leave the floor other.

Other than a pinching feeling from the catheter that kept me from being completely comfortable, I had no pain that I can recall. When the nursing staff came to give me my next dose of pain medication, I told them I didn't want any. They were hesitant but obliged, leaving some pain medication in a cup with my food if I needed it, but I did not. In

fact, I did not have to take any subsequent pain medication at all, including no other doses of the oliceridine through my IV.

I truly feel I would have been fine to go home that night, but I understand it's important for the hospital to observe my recovery to ensure that there were no complications, so they kept me until the following day. They did let me leave in the afternoon.

I was discharged from the hospital on October 5th. My daughter happened to have an appointment that day, which we had made months in advance to get a tattoo as her 18th birthday present for me. She picked me up from the hospital, and we went straight to the tattoo shop. We were there for 4 and a half hours, during which time I walked around, I sat, and I conversed with my daughter.

I laid down to rest in the car for about 15 minutes, only once. The only discomfort I felt after leaving the hospital was a mild soreness in my shoulders, which my discharge summary stated would be normal because of the type of surgery that I had. The soreness went away by the next day, and this was my

experience with this medication.

The only surgery I am able to use as a comparison would be from the previous year in June of 2015 when I had a tummy tuck for cosmetic reasons. Following this surgery, I remember being in much more pain with movement, and the pain medication I was given kept making me fall asleep. I imagine sleep was good for my recovery, but I didn't like it. I didn't like that I would sleep so much and that I often felt groggy and unfocused.

This surgery had a much longer recovery time, which I know that that may not provide the best side-by-side comparison, but it's the only surgery I have for reference.

If I were to have any future surgeries and I'm given the option between using traditional pain medication or oliceridine, I would definitely choose oliceridine. Thank you.

DR. ZACHAROFF: Thank you. Will speaker number 7 please step up to the podium and introduce yourself? And also state your name and any organization you are representing for the purposes of

the record.

DR. BERGESE: My name is Sergio Bergese. I'm an anesthesiologist from Ohio State. My travel was paid today by the sponsor, and my institution received funding for the open-label study. I think I enrolled more patients than anybody in this group, so my intention today was to come with an open mind. I didn't prepare a statement, and trying to make a couple points, trying to help the process

Clearly, the opioids presented a problem that we all are very aware. However, post-surgical pain is going to be very hard to treat without opioids. So opioids do have a role, and clearly looking for different options and alternatives I think is strictly necessary. Clearly, the innovation of drugs like oliceridine I think will have a role in the future. I think approving drugs like this one will give it a strong message to continue this path.

Now, the only two points that I want to make is that I've published more than a few hundred papers. I've done more than 200 trials, mostly in pain. I love data, as you can imagine. Sometimes it's very

difficult -- mostly in pain studies -- to truly get the sense of if the drug works or doesn't work. I think the nurse from Mississippi as well as the patient -- overall, the impression that I got from this drug is that patients do have satisfaction that is above and beyond the classical opioids they will use.

A couple of things that I've seen is probably the kinetics has a little bit to do because the drug acts very quickly. But also, I think the ability to titrate this drug it, it gives the clinician a totally different tool. We understand the side effects and the issues with opioids, but what we don't know and we haven't studied very well is what is this relationship in between doses and side effects and complications? So maybe the minimal drop in titration of the drug may have an impact that is bigger than we previously thought.

Again, thank you very much for giving me this opportunity to speak today. Thank you.

DR. ZACHAROFF: Thank you. Will speaker number 8 please step up to the podium and introduce yourself? Please state your name and any organization

you're representing for the purposes of the record.

DR. WAGNER: Good afternoon and thanks for the opportunity to talk. My name is Deb Wagner. I'm a pharmacist by trade from Michigan Medicine, and my travel has spend supported on behalf of Trevena, but I'm here to speak on my own behalf.

Just to give you some background and credibility of myself, I've spent many years working with pain management at Michigan. I'm involved with the University of Michigan's collaborative for pain initiatives, a Michigan open project. I sat on the executive steering committee for pain management within the health system. I consult for our acute pain service. I hold a joint appointment in the Department of Anesthesiology in the College of Pharmacy for which I teach.

In addition, I work closely with ASHP here in Washington, both for standardized for safety in terms of trying to reduce medication errors, and also as the chair in the past of the medication safety SAG group for ASHP.

So just to begin, I just want to make clear

that I think we all are familiar with the opiate crisis in the United States right now. I know in Michigan, we are number 10 for prescribing of prescription opiates across the country. But I think really our challenge here today is to really look at how we can improve overall management of acute pain in the hospital setting.

With that, I'd just like to give you some background. When you think of how we treat pain in the hospital, from 1995 to 2014, we have not made any significant improvement overall in patients' perception of moderate and severe pain; 75 to 80 percent of patients that we see still complain of inadequate pain. And I really believe we can do better in treating patients.

We know that even 2 milligrams a day of morphine increases overall length of stay, and we also know that there is a very high incidence of adverse effects related to the opiates that we traditionally use. Odereda published a paper looking at opiate-related adverse drug events and found an incidence overall of 13 percent of which 30 percent

were GI in nature.

I think really that's the elephant in the room we fail to recognize, is, really, post-op nausea and vomiting is a significant contributor to patients' dissatisfaction as well as to increased costs in the healthcare system. Both myself and T.J. Gan have conducted surveys with patients looking at a willingness-to-pay model of how much patients would pay to avoid side effects of surgery. And you know what? In both pediatrics and adults, both of them would rather avoid nausea and vomiting and have more pain, which then leads to dissatisfaction among patients for their pain management.

So I guess going on to say, actually, we also have to think of the outpatient population, as more and more procedures are being moved to the outpatient arena. More than 50 percent of surgeries in the United States now are done in ambulatory surgery centers or in an outpatient basis from health systems. This also puts an increased risk of patients who have post-op nausea and vomiting going home with readmission rates right now as high as 10 percent with costs somewhere in

between the range of $4000 to $5,000 for readmission of these patients.

That post-discharge nausea and vomiting rate right now in the United States is about 38 percent. We really have to do better to take care of patients to avoid or minimize side effects that are associated with opiates that we are currently using for pain management.

A couple other things just to say is that I think the other thing we fail to recognize is that morphine has an active metabolite. And since it is metabolized by 2D6 metabolic pathways, we do have a variety of patients that metabolize drugs to a different degree. This separation or difference in metabolism often leads to an accumulation of a metabolite that also has respiratory depression effects. And we can't predict who those patients are at this point in time. We may be able to do some testing, but not enough to actually do point of care at this point for every patient.

I think my last point would be that we need to look at the opportunity to reduce medication errors

because often morphine will be replaced by hydromorphone, and hydromorphone has the risk of having a tenfold medication error discrepancy, where this drug, oliceridine, has a very wide dosing range, and I think will minimize that. But all in all, I think we really are at a challenging point. We can do better for our patients with acute pain, and this is an opportunity to do so. Thank you.

DR. ZACHAROFF: Thank you. Will speaker number 9 please step up to the podium and introduce yourself? Again, please state your name and any organization you are representing for the purposes of the record.

MS. SCHWERIN: Hello. My name is savannah Schwerin, and I'm a nurse and a clinical study coordinator in Jackson, Mississippi. I was a neuro ICU nurse for a year before becoming a study coordinator, which I've been doing for a little over two years now. I don't represent anyone, but Trevena has supported my travel to be here today. They're not compensating me for my time.

I would like to share with you some of my

experiences from my time as a study coordinator for the Trevena oliceridine trial. I had different roles that spanned the duration of patient participation, from consenting patients in conducting screening procedures to administering the investigational product and monitoring for adverse events. Throughout that time, I had many opportunities to gather objective data, as well as listen to patient's feedback regarding their perception of their hospital stay and their study participation.

The patients enrolled in the study at my site underwent various surgeries, including colon resections, hernia repairs, Whipple procedures, and mastectomies. Although their surgeries and post-operative courses all varied, some common threads were apparent among them.

We all know that IV opioids are great for treating acute pain, and of course like many other speakers have mentioned, they have many undesirable side effects. The main concerns of course are nausea and vomiting, constipation, itching, and respiratory depression. In the next few minutes, I will highlight

some of the key observations I had while working on this trial, including those pertaining to the side effects mentioned, as well as some general points regarding patient experience.

Several patients who had taken opioid medications in the past drew comparisons between their experiences with those versus oliceridine, and one of the most common differences noted was that this medication did not make them talk out of their head or feel woozy. Many of them stated how enjoyable it was to be able to visit with friends and family without being drowsy or dazed while also having adequate pain control.

For patients facing diagnoses of cancer or progressive illness, which many were, or even those simply recovering from a relatively uncomplicated procedure, being able to spend quality time with their support systems while having clarity of mind greatly increased overall satisfaction with their hospital stay. Other side effects observably minimal or even absent in many cases were constipation, itching, nausea and vomiting, and the respiratory depression.

In the colorectal surgery population specifically, return of bowel function is an integral aspect of the post-operative healing. For these patients, balancing the need for pain medication with the risk of impeding bowel function can be difficult. For this reason, making an alternative pain medication available to them which doesn't cause such a side effect would be a great value and necessity.

Essentially, many of the patients who shared feedback made note of how much they appreciated oliceridine giving them pain relief without the noticeable unpleasant side effects they would typically expect from opioid pain medications.

In my experience, surgical patients are usually already in an emotionally fragile state. They're anxious and afraid of what is to come. The overall hospital experience can truly leave a lasting impression, whether good or bad. Not having the burden of pain nor the burden of the side effects associated with the pain medications can make an immense difference in their level of satisfaction with the care they receive.

During this trial, the impact of study participation was overwhelmingly positive from my point of view. As a nurse and study coordinator, keeping patients safe while also meeting their healthcare needs is priority number one. Working on the oliceridine trial, I saw firsthand how improving pain management methods can lead to better outcomes.

The need for effective pain relief in the surgical patient population will always be present, and it is of utmost importance to continue the efforts to safely and adequately meet this patient need. Thank you.

DR. ZACHAROFF: Thank you. Will speaker number 10 please step up to the podium and introduce yourself? And as previously stated, please state your name and organization that you are representing for the purposes of the record. Thank you.

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. 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.

New options for pain relief could benefit patients, especially if they're safer than current options. However, they need to be clearly demonstrated to be safe and effective before approval. The data provided are not completely persuasive. It is not clear how well the drug works or under what conditions it works. The low dose was only effective in one of the two efficacy trials when analyzed by accepted pain endpoints. Since replication is the key in science, we can't assume that the lower dose is effective. Perhaps it might be effective for some patients, but the sponsor has not determined if that's true, and if so, which types of patients. However, the discrepancy could indicate that the results was a fluke for one of the trials.

The drug has serious risks like all opioids, and the rates of some adverse events vary between the trials, which could suggest some populations or surgical situations increase these risks. Given the

variation and effectiveness and risk for adverse events between the trials, it is difficult to conclude whether the benefit outweighs the risk.

The sponsor claims that their drug is safer than morphine. It is important for you to challenge that claim because the clinical trials do not yet support it. Some adverse events did occur more often with morphine, but the sponsor was not comparing equivalent levels of pain relief. Overall, the dose dependency of adverse events and pain relief mean that the data do not adequately address these claims.

We commend the sponsor for including relatively large number of black and Hispanic patients in these phase 3 clinical trials. However, there are a few patients that were male or over 65 years old. Differences in weight, comorbidities, and other characteristics could affect the efficacy and safety of the drug.

In conclusion, there are many unanswered questions about what dosages work and are safe for which patients under which conditions. We know that there is an epidemic for opioid use, so these questions

must be answered before a decision is made about whether or not to approve this opioid. Thank you.

DR. ZACHAROFF: Thank you. Will speaker number 11 please step up to the podium? Introduce yourself, state your name, and any organization you are representing for the record.

DR. LeVON: Good afternoon. My name is Hohn LeVon. I'm a clinical pharmacist of 20 some years, many of which were in a hospital. I have not been compensated. Trevena has not paid for my time or air travel. But if people would like to, feel free. I'm more than happy for that assistance.

First and foremost, thank you for your time and what you do to protect the public and to advance the art and science of medicine. After listening to all the information and differences and definitions and approaches on how you measure efficacy and the benefits of using sufficiency versus magnitude alone, as well as different approaches to mathematical analysis, what I would like you to consider now is who you are serving and helping and who you who will benefit from this drug being available.

One population not discussed today, and one that is very common and very important to consider for this medication, are those that suffer from allergies, specifically morphine and hydromorphone allergies. We will all agree that drug-related allergy events are significant and very common occurrences that unfortunately thousands of people die from each and every year. And to that point, I want you to reflect and consider this everyday hospital occurrence, that a patient has a morphine allergy and needs an alternative.

Today, you are only left with hydromorphone and fentanyl. As a pharmacist, I would cringe when I would call the nurse or the physician to alert them of a morphine allergy, and I would just hear them say, "Just give hydromorphone," because fentanyl was not approved for use on that floor or because fentanyl required respiratory support.

Remember, hydromorphone is chemically very similar, and many patients are cross-sensitive, so obviously there's that concern. By approving oliceridine, you would give the practitioners and

patients a chemically unique alternative, but without the morphine allergy risk.

In closing, I want to add that we spent a lot of time today discussing whether oliceridine is better than morphine and whether there is statistical significance to be better than morphine. But when you're allergic to morphine and hydromorphone, morphine is not an option. And being statistically significant better than morphine in efficacy doesn't matter. What matters, as I believe they have shown with their 1800-lus patients, is that it is safe, it is effective, and would be a welcomed new option for a large population of patients that currently don't have an equivalent alternative.

I thank you for your time, and I encourage you to approve oliceridine and take part in advancing medicine and increasing options.

Clarifying Questions (continued)

DR. ZACHAROFF: Thank you.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee will shortly

turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public commentary we just heard.

We do have just a few brief minutes. If anybody had any clarifying questions for the FDA please let us know. We'll give you the opportunity. We're going to keep this very brief so we can move on with the charge to the committee.

Dr. Kaye?

DR. KAYE: Thank you. Dr. Kilgore, I had a question. If you took out the highest dose of this drug, would the conclusions that you presented to us in terms of respiratory effects be the same or different?

DR. MAYNARD: This is Janet Maynard from the FDA. When we analyzed the safety and efficacy, clearly we looked at the 3 doses of oliceridine that the applicant randomized patients to in their trials because we thought it was very important to look to see if there was a dose response for safety and efficacy. And we find that that information is helpful as you think about overall benefit-risk considerations.

Your question about whether or not if we

remove the 0.5, if that would change our conclusions. I don't think so. We know what the results are for the 0.5-milligram dose in terms of efficacy and safety. And as Dr. Kilgore alluded to in her presentation, there were multiple changes to the applicant's proposed dosing during the review cycle, including when the application was initially submitted, they were seeking approval for the 0.5-milligram dosing regimen. So this is a change that happened during the review cycle.

DR. ZACHAROFF: Thank you. Dr. Alexander?

DR. ALEXANDER: And maybe this will come out during the discussion. But it would help me if the FDA could help me at least in my thinking to understand what's necessary for approval. Is this a question of whether oliceridine is safe and effective period, like better than placebo, or better than morphine? Is it a noninferiority question or a superiority question if we're comparing it to an active comparator like morphine?

DR. HERTZ: That's a pretty good question. The standard for approval is evidence of efficacy. And for the most part, analgesics are compared to placebo,

and we don't disagree that there's evidence of efficacy. Then we have to look at safety, and the benefits have to outweigh the risks. So if you look at the risk and benefit of the drug, that's the requirement for approval.

In this case, the objective of developing this novel type of agonist was to demonstrate the ability to differentiate safety and efficacy, and that's why we're looking at it relative to morphine. If we were going to ignore the data for the 0.5 dose, what we would have is evidence of efficacy for the 0.1 in one of the studies, 0.35 in both of the studies, and a safety profile that looks the way it does. But the question then is, if we had lowered the dose of morphine, would we have had the same profile?

That doesn't really answer your question, does it? The fundamental requirement for approving a new drug is evidence that there's a favorable risk-benefit for the product when used in the intended population according to labeled instructions.

DR. ALEXANDER: Can I just make one other question? There was a statement -- I think it was one

of Trevena's presentations -- that the labeling is not going to make statements comparative to morphine.

DR. HERTZ: That doesn't mean the company won't. It just means we won't put it in the label.

DR. ZACHAROFF: Just two more, and then we'll move to the charge to the committee. Dr. Goudra?

DR. GOUDRA: Hi. Dr. Goudra from U Penn. One or two questions. Unlike morphine, oliceridine is metabolized through the cytochrome P450. And I see about 10 percent of the patients in the information given by Trevena are kind of low metabolizers. Did the FDA analyze the data between normal metabolizers versus low metabolizers in terms of adverse events?

DR. HERTZ: I don't think we received any data looking at different phenotypes for the CYP enzymes, but perhaps we did.

DR. VIOLIN: I'd be happy to provide extra data if that would be useful to you.

DR. GOUDRA: [Inaudible - off mic].

DR. VIOLIN: Oh, the extensive metabolizers. We did evaluate the pharmacokinetics as well as the safety of oliceridine in extensive versus poor 2D6

metabolizers. And while the clearance is slowed in 2D6 poor metabolizers, because the drug is given as needed, what happens is they dose less frequently. So the maximum concentration of Cmax did not change in the phase 3 studies, independent of 2D6 status.

I'd like to clarify one other point as well, which is we tried to be clear that when we were developing oliceridine, the primary endpoint, the prespecified primary endpoint that did succeed in both studies for both point 0.1 and 0.25 was something that we believed the agency was not opposed to.

They told us at the end of phase 2 meeting they did not object to it, provided there was additional evidence to support the findings, which we think we have and have shared. And that that demonstration of efficacy would be sufficient to show the drug works. And the overall safety profile that is characterized as a holistic assessment would be put in context of efficacy demonstrated versus placebo.

All the comparisons to morphine were a scientific question and an important scientific question. But we did not design the studies to support

approval in that way. That's why the endpoints were structured the way they were. That's why the studies were powered the way they were. And that's why we've tried to keep those questions separately.

The data we think that supports approval is very robust and statistically significant, and we agree that some of the improvements, while very encouraging, do not meet regulatory thresholds. And that's why we say we don't believe that they merit comparative claims in labeling, but that's separate from the approval question.

DR. ZACHAROFF: Thank you.

DR. GOUDRA: Just one more question.

DR. HERTZ: Excuse me. I just want to clarify. My understanding is that the comparisons with morphine were part of the prespecified statistical analysis plan. And presumably had they been successful, you would have sought to have them in labeling?

DR. VIOLIN: Our understanding of the key secondary endpoint, which was the respiratory safety burden, because it was not validated, that was not

going to be acceptable for safety comparison. Nonetheless, we thought it was important to test. We thought we generated a lot of interesting data, and it's something that we would welcome further discussions with the agency in terms of postmarketing studies.

DR. GOUDRA: You're not asking for approval in pregnant patients do you? I don't see any data on --

DR. VIOLIN: No, we've not studied that.

DR. GOUDRA: Okay. Thanks.

DR. ZACHAROFF: Just two more. Ms. Phillips?

MS. SHAW PHILLIPS: Thank you. In the agency's discussion, I think there was a comment related to the phase 2, indicating that in addition to the prespecified rescue medication, there were other medications that might have made assessment of acceptability of the pain control, difficult to assess.

Could you provide additional information on that?

DR. MAYNARD: Janet Maynard from FDA. Do you mean in the backgrounder there was --

MS. SHAW PHILLIPS: There was a comment this

morning about --

DR. MAYNARD: But I think that was in reference to the phase 3 studies.

MS. SHAW PHILLIPS: Okay. Could you comment on those? I think clarifying that endpoint of not needing any rescue medication and all that is really important.

DR. TRAVIS: Yes. The sponsor's original analysis ignored use of -- James Travis, statistical reviewer. The sponsor's original analysis ignored the use of non-protocol specified, and there were quite a few people who used it.

I have a backup slide. Is it numbered from the -- I think slide 36; 37 then. There we go.

This is the rescue medication that was used in the phase 3 program, so anything that wasn't etodolac was not taken into account for their responder definition. The analyses I presented included them as non-responders because we don't see the point of discriminating between etodolac and anything else.

MR. PETULLO: This is David Petullo --

DR. VIOLIN: If I might just respond very

quickly, I just wanted to remind the committee that the data we presented in our core for the primary endpoint did include non-protocol specified --

MR. PETULLO: I just want to put out that this didn't change our overall conclusion. It might have changed the numbers slightly, but it wasn't a major issue.

DR. VIOLIN: When the agency brought this up in review, we agreed. We included in the analysis that conclusions did not change.

DR. ZACHAROFF: Thank you. All right, lastly, Dr. Fischer?

DR. FISCHER: Thanks. I'll be quick. I'm Mike Fischer, Brigham Women's in Boston. In terms of the respiratory side effects, we already discussed the differences in how those were defined, and that's been covered. Thinking about the kinds of patients likely to be receiving this in general practice, were there any analyses of the respiratory safety events profile focusing on patients with any kind of preexisting risk?

I know there were some patients with sleep apnea. I don't know if patients with preexisting

pulmonary disease were completely excluded. I don't know if you have anything on that.

DR. MAYNARD: As Dr. Kilgore mentioned, we focused on the respiratory safety in the phase 3 trials. And generally, as the sponsor has mentioned, the populations in phase 3 trials tend to be slightly on the healthier side usually because they frequently don't have as many comorbidities as some other patients in practice.

The sponsor did provide data from study 3003, which has information about respiratory safety and what they thought would be a more real-world setting. The problem with that study is there's no comparator, so it's very difficult for us to make any definitive conclusions on what the respiratory safety would look like in that sort of setting because we really don't have comparative data to assess that.

DR. ZACHAROFF: Okay. Thank you.

We will now move to Dr. Sharon Hertz, who's going to provide us with a charge to the committee.

Charge to the Committee - Sharon Hertz

DR. HERTZ: So you've heard a lot today about

this new product. You've heard about the applicant's data and interpretation of the safety and efficacy for this novel G-protein ligand biased agonist of the new opioid receptor. And you've heard our interpretation of the data and where those differ.

We acknowledge that the nonclinical and experimental data were supportive that there could be a differential effect on some of the adverse events and the clinical efficacy, but where we disagree is how well, if at all, those were described in the clinical studies. And we also have some disagreement with respect to understanding the relative efficacy and safety of the active comparator. But it was brought up that the standard for approval is not that a new drug has to be the same or better than an existing drug. It should be approvable on its own merit based on the overall data and the risk and benefit balance for that product.

So as we go through the questions -- there are fairly standard questions now that many of you can probably recite -- in terms of what you think about the efficacy, the safety, what you think about the public

health risk, scope, and novel opioid, and what you think about the overall balance and whether or not it supports approval, please consider that in the context of your experience and how you understand the product will be used based on what's been described today.

As always, while the vote is very interesting, what's even more interesting is to hear the thoughts that you have in response to these questions and the thoughts that you have that support how you ultimately vote. Thank you very much for being here today.

Questions to the Committee and Discussion

DR. ZACHAROFF: Thank you. So as we start to address the questions, I would like to encourage all of the panel members to participate. I'd like to encourage you to give your thoughts and perspectives with respect to the question without saying how you're going to vote; really, just to give your impressions about the question at hand and what your thoughts are, and to use your expertise, to the degree that you can, to apply the discussion questions to your specific areas of expertise, and give your perspectives about what you really think given your area of expertise.

So with that, we will move on to the first question. Discuss the efficacy of oliceridine and whether the data provides substantial evidence for efficacy of oliceridine for the proposed indication of the management of moderate to severe acute pain in adults for whom an intravenous opioid is warranted.

Panel members, discussion?

DR. ZELTZER: Are you going to go around the room?

DR. ZACHAROFF: We could go around the room. You can turn your cards. What would you like?

Dr. Solga?

(Laughter.)

DR. SOLGA: Honestly, I wasn't prepared to make a statement, but there's some evidence for efficacy. There's no doubt about it. There's the step-wise dose response. There's no doubt it's an effective medicine versus placebo. I'm still struggling with the context and whether or not that's acceptable in the overall scheme of regulatory approval.

DR. ZACHAROFF: Thank you. Dr. Zeltzer?

DR. ZELTZER: It seems as though there are two issues in terms of efficacy. I think that the product has been shown, at least in terms of comparison to placebo, efficacy in the situation for acute moderate to severe pain, but in a relatively healthy population. Given the procedures that were studied, those procedures are generally performed not in the kind of population that one of the audience had talked about, the surgeon who's seeing obese patients who have heart disease, the multi- complicated, complex patient.

I guess in the relatively healthy patient for a relatively non-major surgical procedure, I think efficacy has been shown, at least to my satisfaction. Now, the request is for up to 40 milligrams, and I think one of the slides that you showed, if you look at the maximum, or maybe it was FDA's, it was 24 milligrams even though the request is for 40-milligram maximum in that time period.

So I don't know if that creates a problem, but if the indication in terms of efficacy is for all kinds of surgeries or all kinds of situations, short-term moderate to severe pain, I guess I would

feel more comfortable if there were a study in a more complex population because that's the population, if you look more broadly, that this drug will end up being used.

So it's a question. And I'm sitting here like this because I think you did show efficacy for the populations studied.

DR. ZACHAROFF: Thank you. Dr. Litman? Again, we're limiting this just to the discussion around the efficacy.

DR. LITMAN: Thank you. Ron Litman. I do agree. I think that the phase 3 study showed efficacy, but I have a couple of thoughts about that. The first is that this is not real life. Real life is just like we talked about before where you titrate. And in the clinical setting, when we're treating a patient with pain, it's never just one dose. It's many doses. It's consideration of lots of different factors.

Unfortunately, there's just no way to find the truth behind what will happen with this drug once it's being used. It takes many different patients over years. So clinicians will ultimately decide for

themselves.

The second thing is this is really just based on one phase 3 study and a couple of open labels. I was a little concerned during the public comments when several of the commentators talked about both nurses and patients the way they were approached. And I would hope that this was the open label, not the blinded study, how here's this miracle drug that's going to give you less nausea and make you feel so much better than the real drugs we use. I mean, if that was truly in the phase 3 study, that's the exact opposite way to do a clinical study, of course.

The third aspect I wanted to comment on is the marketing, and that's one of the things that I was thinking about before -- and Sharon alluded to it before with her comments about what the company could say about the drug. As the law stands now, a drug company can market a drug based on truthful information, depending upon of course the district you're in and whether or not it's on the label. But even in the districts where it was found by the Caronia case to be free speech, it's only free speech if it's

truthful.

So if the truth is that it's not better than morphine, then they shouldn't be able to market it as such. Now, we all know in the real world that doesn't always occur. History has shown that does occur in many different products. So those are my comments, and I'll let other people contribute.

DR. ZACHAROFF: Thank you. Dr. McCann?

DR. McCANN: Dr. McCann, and I'm speaking up because you asked everybody to speak up. I think the drug is efficacious certainly against placebo. There's been no evidence at all to suggest that it's not.

DR. ZACHAROFF: Thank you. Dr. Terman?

DR. TERMAN: Thank you. And I also think that it shows efficacy, certainly the 2a fixed dose shows that you can get more pain relief if you push the dose. However, if you asked me if there's any advantage over morphine, I'd say I don't have any idea because I think all of the PCA studies more clearly by chance are designed easier for patients to titrate to their sufficient level of analgesia. If you set the dose such that they only hit it once an hour, you're going

to have an awful hard time titrating because they're going to have to decide, well, am I willing to risk the side effect?

The other thing that I like about the efficacy is the rapid onset. It really does appear to be working very quickly, 5 minutes in some other data. That should be useful for a patient who's got a 6-minute lockout on their PCA.

DR. ZACHAROFF: Thank you. Dr. Shoben?

DR. SHOBEN: I have a couple of comments about efficacy. The first is to say I actually really liked the responder. In point, we talked about it at a previous advisory committee, this problem of imputing the scores for patients with rescue medications. And this sort of responder endpoint both addresses that concern and gets at the idea that the sponsor talked about, about treating pain disorder sufficiency and not trying to get to a goal of no pain, which I think most people at least would agree that's important.

So if you agree with the responder, then I think they have met efficacy for both 0.1 and 0.35 dose. That said, it's clear to me that there are

questions around 0.1 dose and whether or not that efficacy compared to placebo would be enough to -- that that benefit would be enough to outweigh any potential risk of 0.11 I think the efficacy for 0.35 is certainly stronger, particularly using the actual numerical scores with different imputation as demonstrated by the FDA reviewer

Yes, so I think those are my comments. Thanks.

DR. ZACHAROFF: Thank you. Dr. Goudra?

DR. GOUDRA: Dr. Goudra from Penn medicine. A couple of things. People are talking about efficacy compared to placebo. In real life, we don't give placebo. We use morphine or dilaudid or whatever it is. From that point, it looks like if the question is substantial evidence for efficacy and the dose that Trevena is seeking approval for, I don't think there is substantial evidence to show that it is as effective as morphine. Like it or not, that's what we should be looking at in terms of efficacy, not the placebo.

Maybe if the dose is increased to improve the efficacy, it probably loses the selectivity in terms of

G-protein protein versus beta arrestin, and maybe they'll address [indiscernible] go up. That's my feeling.

DR. ZACHAROFF: Thank you. Dr. Alexander?

DR. ALEXANDER: Thank you. John Alexander from duke. I too think there's clear evidence of efficacy versus placebo. There's further evidence from the dose response within the oliceridine doses. It's less clear to me whether there's an efficacy benefit, or equivalency, or noninferiority of oliceridine compared to morphine.

I've just been thinking, the whole premise of the development program that we heard is that oliceridine is going to be just as effective as currently available narcotics -- they studied it against morphine -- but with improved safety, which we're going to come back and talk about further.

I've been thinking through that the key question about whether there's roughly equivalent or noninferior efficacy compared to morphine, it seems to be dependent on which method of efficacy analysis is chosen, the one the sponsor did or the one that the FDA

did. And I've been thinking about and haven't figured out yet which one is more clinically relevant. Which one's more relevant to how we dose narcotics or how people who do dose narcotics like this -- I don't -- dose narcotics clinically, using a threshold or a magnitude of effect?

DR. ZACHAROFF: Thank you. Dr. Fischer?

DR. FISCHER: Mike Fischer, Boston. Coming back to the question of substantial evidence of efficacy, I'd echo Dr. Shoben's point that the substantial evidence threshold seems harder to justify for the 0.1 dose. And because the other component of the application is the 0.35 dose, the thing I'm grappling with is do we have substantial evidence when we think about the range of patients who will be getting this in usual practice? Again, thinking about some of the public comments, the patients who've been on chronic opioids, the patients who are obese and getting surgery, and some of the others, do we have substantial evidence of efficacy for those kinds of patients because later we'll be of course weighing that against the safety. So those are a couple of the

points I'm chewing over.

DR. ZACHAROFF: Thank you. Dr. Kaye?

DR. KAYE: Alan Kaye from LSU, New Orleans. I think it's clear that there's evidence for efficacy versus placebo. I just would say that 15 years ago, we moved away from morphine to use other agents in this setting because we didn't think morphine was so great. So not to confuse everyone, but it really wouldn't be something that we would measure in our practice against morphine. We would probably look at things like dilaudid and some of the other agents that have better profiles.

DR. ZACHAROFF: Thank you. Dr. Warholak?

DR. WARHOLAK: I agree with some of my colleagues that the 0.1 dose, the efficacy is harder to show. In the FDA briefing packet on page 12, it indicated that the 0.1 dose was not statistically significant but statistically significantly better than placebo. Now we're not asking for approval for the 0.5, so that only leaves the 0.35. So I'm not sure exactly where that leaves us.

DR. ZACHAROFF: Thank you. Dr. Solga?

DR. SOLGA: I'm sorry. I wasn't quite ready to speak earlier when you called. Just to follow on to an unprepared statement maybe as a flip statement, many others have pointed out that maybe placebo just isn't the right comparator, even though that's the statutory expectation. As Dr. Goudra points out, nobody prescribes placebo.

Earth has many pharmacologic and non-pharmacologic opportunities for pain management. Not to sound flip, but one of my liver colleagues who had a foot surgery and was suffering in pain, couldn't sleep at night, and his Percocet ran out. I said, "What did you do?" And he said, "Drink scotch, and then I drank more." So that also has a dose-response curve that folks recognize and use.

So the reality of 0.1, 0.35, and 0.05 differed on dose-response curve efficacy to placebo is important, but almost, gee whiz, so what, compared to the big picture of benefit-risk considerations.

DR. ZACHAROFF: Thank you. Ms. Phillips?

MS. SHAW PHILLIPS: I think a lot of my comments have already been made, but I think the PK

shows that this is a drug that can have a very fast effect. So it has an effect, and I think there's a benefit there on the whole range of sufficiency. If patients can get that effect and be able to manage their pain in a way that is patient-centric, where they have control over that decision point, and ultimately use less of an opioid medication, that's a good thing.

So I think in today's era of multimodal pain management and trying to minimize the bad effects of any medications that we're on, if the patient has more control over that and gets a suitable level of efficacy in a way that minimizes the side effects, even if that's due to a lower dose, I think there is an efficacy benefit there.

DR. ZACHAROFF: Okay. And my comments mirror pretty much what I've heard all of you say, so I don't really have anything to add. But just to summarize to make sure I got this right -- I'm sorry.

Mr. O'Brien, I didn't see you there.

MR. O'BRIEN: I don't have much to add to it, except I would say from my patient perspective, I agree. Substantially. I struggled with the word

"substantial" that's there for the evidence. However, I would say from a patient, give me 0.35. I don't want 0.1. Don't bother with that. It's wasting my time. And I'm very fearful of getting 0.5. There's a threat there that I see.

DR. ZACHAROFF: Thank you.

Just to summarize the comments to make sure we captured them adequately, if I leave anything out, please let me know. By and large, people are satisfied that from an efficacy perspective, oliceridine demonstrated efficacy in healthy individuals but not necessarily complex patients with multiple medical problems. And while it was better than placebo, that's probably not surprising because anything would likely be better than placebo. And in managing pain, there really is no situation where you use a placebo to manage someone's pain.

From a real-life perspective, the likelihood is that this drug will be titrated. So it may be difficult initially to wrap our heads around how much of this medication is actually used, especially when we're not necessarily recording how many times the

patient presses the button. And if they can press it every 6 minutes and get a dose every 6 minutes, it may take a while.

So real life is going to be a titration kind of situation and how much medication is actually needed to treat different people's pains for different reasons may be very different.

People mentioned the fact that the relief is dose related. I think the general consensus of the panel was that there weren't really many impressions about superiority to morphine in this case. There was superiority to placebo.

The rapid onset definitely is a quality of this medication that poises it to be a value in patients who have an intravenous access, who do have acute pain of this severity. There still remains the question about the 0.1-milligram dose and its ultimate efficacy, that the data presented wasn't really substantial to make people overwhelmingly feel that the 0.1 milligram was going to save the day by itself and it might end up being the point 0.35. As we heard Mr. O'Brien say, he said, "Give me the 0.35," and let's

get down to brass tacks.

I guess lastly, the overarching question is, is evidence for use in real-life patients that we're likely to see enough to give us confidence with respect to the efficacy?

That's my summary of the discussion for question 1. Did I leave anything out?

(No response.)

DR. ZACHAROFF: Okay. So we're going to move on to discussion 2. And good job, by the way, of not saying anything about voting. We want to keep it just to the discussion, so kudos for that.

Question 2, discuss the safety profile of oliceridine and whether the safety profile of oliceridine is adequate to support approval of oliceridine for the proposed indication of the management of moderate to severe acute pain in adults for whom an intravenous opioid is warranted.

We really want you to think specifically about these four categories from a safety perspective: general safety, hepatic safety, respiratory safety, and QT prolongation perspective.

To save me from calling on anybody, anybody have anything to say? Dr. Litman?

DR. LITMAN: Thank you. Ron Littman. Just going down the list here real fast, the database of I forget how many -- a couple thousand patients, there's just no way to know, honestly, what the right number is. It seems, my general gestalt from looking at the data and looking at the number of patients, that it is relatively safe. And relatively is a really hard term to define here because we're thinking about it compared to placebo, but we're also thinking about it compared to other opioids.

Hepatic safety is a little bit alarming because of a couple of signals in the data, and I don't have the expertise to be able to reasonably comment on that for sure. But I would be very interested in further phase 4 studies looking at what happens down the line when more patients take it, and do these few patients that popped out before that we discussed, is that really a signal? Is that really different from other drugs?

Respiratory, again, we talked about the

hypercapnic test, and that's just such an artificial test. It really is just so preclinical in a sense even though it's on humans. Honestly, Dr. Webster, I'm sorry. I'm not convinced that the way that it was conducted was really rigorous or accurate. It may have been. I just couldn't tell from this data.

But on the other hand, just looking at all the data cumulatively, I don't have any considerations, except if further studies or further experience showed that these doses, which we think may have been less efficacious than morphine, in real life that we have to use higher doses in order to control our patient's pain. And that we don't know. And I don't have any concerns about QT prolongation.

DR. ZACHAROFF: Thank you. Dr. Higgins?

DR. HIGGINS: I could not help but be persuaded by the FDA analyses. I find them highly persuasive. And I can't also disentangle the comparison to morphine as I think about all the data cumulatively. With respect to hepatic safety, I find the same frequency of problems between oliceridine and morphine and the treatment groups. With respiratory

safety, no statistically significant difference between morphine, and again, insufficient data I think to really evaluate this.

Under QT prolongation, I would have liked to have seen more ECG data, and I think that was inadequate. And I just think overall there was not enough data to really evaluate that as well. Those are my statements on the four areas.

DR. ZACHAROFF: Thank you. Dr. Goudra?

DR. GOUDRA: Dr. Goudra from Penn medicine. A couple of issues here. One, as anesthesiologists, we do end up loading up these patients interoperatively to prepare them for post-op pain. So as a result, we do not necessarily titrate them in the 0.1 or 0.25, whatever. I don't know whether Trevena wants us to do that interoperatively like we do [indiscernible] morphine.

If we do that, unlike morphine, there is a problem of 10 percent of the population who only half metabolizes. As a result, their effective concentration is almost twice. So would they be subjected to more problems as far as safety's

concerned, whether it is respiration or -- so that's one aspect.

Second, yes, in clinically recommended doses, hepatic safety and QT prolongation may not be an issue. But considering it is an opioid and it will be subjected to the same abuse problems like other drugs, if somebody either accidentally or deliberately injects it, will we have the same QT prolongation related problems where we add cardiac and hepatic toxicity over the respiratory depression already? Thank you.

DR. ZACHAROFF: Thank you. Dr. Terman?

DR. TERMAN: Sure. Thank you. Let me say that I am a big fan of the agonist biased story, and I followed it in my basic science lab, participating a little bit since Dr. Bond's first beta arrestin knockout paper in Science showed a potentiation of morphine, and actually along with that suggested a decrease in tolerance.

I'm very interested in this class of drugs, and I'm pleased to see that the work continues. In terms of other, this is the first. There's a BCM [ph] compound and a whole list of compounds from

Scripps [ph] that have -- and I'll talk about what I know best -- some association with respiratory depression; that is the decreased arrestin activation seems to be correlated with a safer experience, at least for rats, mice, and monkeys. And it hasn't gotten to humans quite yet.

However, having said that, although I did like the new slide that showed the better analgesia than morphine early on, despite a similar respiratory depression as morphine, whether or not cold pressor is a clinically relevant test, I've used it as such, and so I have a hard time pretending that it's not. But I don't think that there's anything in the more recent clinical studies, as I said before, because of relative more morphine being given. I don't think we can say anything about the respiratory safety.

What I was pleased about and what I asked about was whether this rapid onset drug that does cause euphoria might have any more abuse potential than morphine, a slower onset drug. And everyone seemed to agree that that was not the case. So that's a good thing for me.

In terms of the hepatic safety and QT prolongation, I don't know. I have to just trust the experts. So that's the end of my comments. Thanks.

DR. ZACHAROFF: Thank you. Dr. McCann.

DR. McCANN: I think all the data that's been presented demonstrates that it appears to be pretty safe, but my concern is that they haven't met the threshold. So I asked that earlier question about 350 people and whether that was just a number pulled from thin air or actually had some statistical basis, and I guess it's got a very soft statistical basis. But they haven't enrolled 350 people at the 40-milligram per 24 hours dose, which is what they're asking permission for.

It gets back to When I look at the other safety aspects, the safety database seems fine. The hepatic, I can't really ascertain but it appears safe. Respiratory, I'm not worried about. But the QT prolongation, I think in the real world, people are going to titrate this to effect because that's what we do for other narcotics. So it would be relatively few patients that would get more than 3 milligrams, but

there might be some that had prior exposure to narcotics that would get the 6 milligrams. We don't really know enough about that in terms of QT prolongation.

So I think it would be -- since Dr. Hammer and others have mentioned that this is not a perfect drug, it may be an improvement. I don't know that it's necessary to cut corners before we get the adequate data. And again, to go to Dr. Zeltzer's point, we don't know anything about how this drug behaves in elderly great-grandmothers. Thank you.

DR. ZACHAROFF: Thank you. Dr. Fischer?

DR. VIOLIN: Can I make one comment? I just wanted to

reiterate that in ATHENA, we did enroll hundreds of patients over the age of 65. We enrolled patients with sleep apnea. We had a very high enrichment. We really care about this problem, so we have those subpopulations and didn't see any difference in the safety profile. I just wanted to remind you of that data. Thank you.

DR. McCANN: Okay.

DR. ZACHAROFF: Dr. Fischer?

DR. FISCHER: Great. Thanks. Mike Fischer from Boston. The question I think to me is the adequacy of the data, especially, picking up on some of what Dr. McCann was just talking about, the overall flavor of the presentations, the public comments as well is really focused on the idea that this is going to be a medication. I realize that there will be what's said on the label, but that this is likely to be used for those patients who are difficult to treat. I mean, that's the flavor we've been getting all day, that we need something for those difficult to treat patients. And those are patients who, for a variety of reasons, are either likely to have more complicating factors even then in the open-label study or end up -- because we're going to be titrating in clinical practice, with much higher doses.

So in thinking about some of the signals we have that can't quite be spoken to authoritatively, especially those looking at the FDA presentation where there is a better respiratory safety signal because we're not using as potent an analgesic dose of

oliceridine in the trial compared to morphine, I worry that the safety database we have at present does not represent the dose range and population that will be getting this once the drug's been in clinical practice for a while.

We can't do everything. That's what phase 4 studies are for, but it does make really salient the question Dr. McCann was raising, do we have enough information on the patients who are going to end up getting titrated to pretty substantial exposures of this drug out in real-world practice.

DR. ZACHAROFF: Thank you. Dr. Zeltzer?

DR. ZELTZER: There was one point that maybe I missed. In your presentation, at least by this slide, or again maybe -- you want approval for up to 40 milligrams. And I thought the actual data presented, the maximum was actually 24 milligrams. So in terms if we're thinking safety -- can somebody -- can you speak to that?

DR. VIOLIN: I'm happy to if that's okay. so the FDA was very clear. They wanted to see 350 patients with the highest and longest exposure to

determine what the maximum daily dose should be. We had proposed -- as you've heard, we've been in discussion with the agency. Most recently, we propose 40 milligrams as the median of exposure in that group. The FDA has pointed out the 27 milligrams is the minimum. So that's the number at which there are 350 patients, have had at least 27 milligrams in the first day.

Now, in the ATHENA population, that's where multimodal analgesia was used, so that most closely reflects how you might use this in your practice. 27 milligrams was -- sorry. About 80 percent of patients used 27 milligrams or less.

So we're proposing 40. We consider this a dialogue with the FDA. Anywhere in that range is going to satisfy the great majority of patients in the multimodal context.

DR. ZACHAROFF: Thank you. Go ahead.

DR. ZELTZER: I'm sorry. So again, I mean, as I was hearing the data, there was nothing that stood out in any major alarm way, except I couldn't get over that the population in which the data were obtained

were not the usual -- not usual, but not the complex population that this will be used in. So we don't have safety data on the population that needs -- that the indications are for, or that broader range.

That makes me concerned about the safety. And obviously, you won't really know until it gets rolled out in the real world, and you have a phase 4. But still, the studies that were presented were in a relatively healthy population overall, and the PCA, the last study, we don't have enough data on who the population was, the age, the risks, the other medication. So it wasn't designed for a safety trial in that sense.

So that's the part that makes me just a little worried in terms of safety, even though the data presented, as you presented it in that population, seemed okay, relatively.

DR. ZACHAROFF: Dr. Alexander?

DR. ALEXANDER: Thank you. John Alexander from Duke. Just to go walking down the four items, the 350 patients with the projected mean duration of treatment seems largely arbitrary and historical, and

it's probably adequate. And I think that adding a few hundred more relatively low-risk patients is unlikely to add much.

Regarding hepatic safety, it doesn't seem to be an issue to me. The only cases of concern come from an uncontrolled, broad, relatively real-world study with other potential explanations for hepatic injury.

The pattern of opioid related -- with that I'll call respiratory and GI safety events -- seems to favor oliceridine.

But whether this is a drug effect or a dose effect isn't entirely clear to me. If you were to give a lower dose of morphine, you would also have a pattern of less respiratory and GI side effects, potentially. So this dose equivalency is very important.

Then related to cardiac safety, I think we need to conclude that there is a modest effect of oliceridine on the QT interval. We see that in the dedicated QT study, which is the purpose of doing it. And if there's as much effect as our active control that we typically use to pick out some QT effect, really interestingly, this effect is delayed an hour

after the PK effect, and we don't right now know the explanation for that disconnect between PK and peak QT effect.

I personally don't find the APOLLO studies or ATHENA particularly helpful. The APOLLO studies are still a highly selected, low-risk population who got -- I'll come back to this -- selected doses of oliceridine, so I think dose is important. They had EKGs at 1, 24, and 48 hours that were interpreted by the sites. And site interpretations are likely to increase noise. Even if going in the direction of overestimating QT interval, this won't help detect a modest signal if that's what our interest is in.

So given the issues related to efficacy and safety and dose, I have concerns that higher doses will be quite -- I expect that higher doses will be used in practice in the broad range of patients who will get this than were used in the QT study or the APOLLO studies in higher-risk patients with more concomitant QT prolonging medications, and that the cardiac safety of these higher doses is unknown.

I don't know that there's a safety signal in

these higher-risk patients. I just don't think we know. And a big part of why we don't know is this disconnect between PK and the QT effect.

I'll just comment, in ATHENA, where there were more real-world patients, patients received a mean of 19 milligrams with a range of point 0.9 to 224 milligrams over a 1 to 142 hours. And there were cases of more QT prolongation in ATHENA, but it's an uncontrolled population, so we don't know whether that's due to oliceridine or one of the other concomitant effects.

Then on the other hand related to QT still, we have not seen significant ventricular arrhythmias in a thousand or so patients who've gotten oliceridine, and a large proportion of them more real world. And in practice, many of these patients -- not all but many, particularly the higher-risk patients, will be monitored with telemetry.

Now, I don't have a great sense for what proportion of patients getting all oliceridine would be monitored, but at least the highest-risk patients probably would be.

DR. ZACHAROFF: Thank you. Dr. Solga?

DR. SOLGA: I'm okay with the safety database, the hepatic safety and the QT prolongation. The story of the G-protein agonism was one of improvement in respiratory safety and also nausea and vomiting. I don't know what to make of the respiratory safety, and I'm concerned that the impression that it's safer could lead to less vigilance when it's actually used on wards.

The most important way to find out if your patient is breathing is to look at them. And it's extremely important that folks respect the potential of any of these medicines. And the impression that it's safer without firm evidence that it is could actually be counter-productive.

I am more impressed, however, by the study drug's improvement in vomiting. I think that's been somewhat under-discussed, and I add that as point E. Vomiting is not so much a comfort issue. It really is a safety issue. Particularly when folks are sedated, vomiting could have devastating effects. And clearly, there is a dose-related reduction in vomiting with

study drug compared to morphine. And even at 0.5, there seemed to be less vomiting. So that does support that hypothesis works.

DR. ZACHAROFF: Thank you. Mr. O'Brien?

MR. O'BRIEN: It's always when we get to these questions that the real difficult charges come out. It's interesting to me when we're asked for efficacy, it's for substantial evidence, but when we get to safety, it's adequate support; we sort of shift. And when we're talking about efficacy, it's in comparison to the placebo, but if we're talking about safety, we're not talking about the placebo because in terms of safety, no, we had adverse events. So compared to placebo, if we're using the same thing as efficacy, no, it's not safe from that perspective.

However, assuming that we're talking about comparative here as opposed to when we're talking about efficacy, my take-away is very much what I've heard already. And as you know already, I was concerned with the respiratory safety.

I thought it was very interesting listening to my fellow patients and those that thankfully serve

those patients, we heard about itching and we heard certainly about nausea and vomiting. I think that is a very important issue in terms of the safety. But we heard other things with constipation that really wasn't explored. I don't know if that's safety and it's going to save us from addiction. I don't think there's any evidence for addiction in terms of being safe. We've shown that it's not. It's going to be the same actually for abuse and addiction. So from that safety profile, I don't see any change to that. that.

Even from respiratory, with the FDA analysis, which I go along with, I'm not quite -- as I explained with my own particular situation and the patients that I know, I don't see any evidence yet that the hypothesis that there will be improved respiratory has been shown, substantially for sure. So that's to me the way -- it's safe, but no safer than anything else.

DR. ZACHAROFF: Dr. Kaye?

DR. KAYE: Alan Kaye from LSU in New Orleans. I just wanted to make another comment. As we look at this, we have to also consider drug-drug interactions. There's a paper from 2012 by Nagel Anesthesiology

looking at non-cardiac adult patients for which they measured QT prolongation. There are hundreds of drugs listed that can cause QT prolongation.

So the point being, that study showed 1 in 25, 4 percent of people had significant QT prolongation. So if you are throwing in another drug that would be used in acute pain in all comers, you have to consider drug-drug interactions.

I would say just globally, I agree with what everyone has said. We have some data. Some of it's pretty good; some of it is not as robust as we would need to really feel comfortable. So it's kind of a difficult challenge for us today.

DR. ZACHAROFF: Thank you. Dr. Alexander, did you have anything else? No.

So just before I summarize, I just want to add a couple of my own comments, and thanks for the good discussion. In the real-world realm of things, a an anesthesiologist, I certainly realize that the way I look at things in an acute pain situation post-operatively is that the pain management is sort of a handoff, and a handoff, and a handoff.

When the patient leaves the operating room and the anesthesiologist is going to make sure that there's some level of analgesia there to get the patient to the PACU. In the PACU, there's going to be some measures that are taken to make sure that the patient's comfortable and pharmacologic measures are going to be taken. And then when the patient is discharged from the PACU, and then they go up through the floor, then a PCA might be implemented, or maybe the PCA might be implemented before the patient is discharged from the PACU.

Somebody earlier said something that really struck a chord with me, and that is that the way the dosing for this medication would be done is based on what medications they had already been given. And I'm not 100 percent confident that I know that if I loaded a patient up with fentanyl before I left the operating room, and then got a bunch of dilaudid in the recovery room, and then we put them on the floor with this medication, what that safety profile edge is.

The scenario that I'm describing to you, I think as an anesthesiologists, we'll be able to nod and

say that's exactly what happens. It's multimodal opioid analgesia, let alone multimodal analgesia in total. So it may be outside the context of the presentations today and the briefing materials, but from a premise safety profile, I worry about what happens on the front end when the patients have been loaded with opioids, which they will have before this medication is given to them, and what potential effect from a drug-drug perspective that might have, because we know there could be crossover respiratory depression when dose meets dose and blood level meets blood level after the fact.

I don't know what the answer to that question is, and I didn't hear it discussed today. So that's my perspective.

Just to summarize the discussion before we take a 15-minute break, from the perspective of the safety profile as we see posed in the question, my summary would be that the general consensus is that it's relatively safe overall, and that from a hepatic perspective, it's probably similar to morphine or it may be no more dangerous than morphine in the majority

of patients.

And there is insufficient data to really conclude one way or the other based on what we've seen about whether there's increased safety over morphine, especially because of the confounding that we heard about with respect to other medications given to the patient.

In increased doses maybe due to abuse or medication error, it's likely to be as dangerous as another opioid with respect to opioid-related side effects? Agonist bias is definitely a good thing. Looking at new ways and more specifically tailored approaches is definitely a good thing from a safety perspective, and I guess you have to start somewhere.

There was a sense that cold pressor tests and things like that aren't necessarily real-world valuable in terms of patient experiences. I guess from a safety perspective, again, speaking as an anesthesiologist, we measure end-tidal CO2. We measure oxygen saturation in real time. I'm not 100 percent sure myself about what the testing that was done on young healthy volunteers really has to do with hypercarbic drive.

We did hear some discussion about the fact

that 350 subjects weren't identified within the therapeutic dose range for the maximum daily dose, but I don't know that anybody around the table really has a sense of the fact that if it was 250 versus 350 or 270, whether that would really make a difference at the end of the day.

We did hear discussion about the fact that higher doses are likely -- or there is at least a sense that higher doses may be likely to cause QT prolongation, and at least there might be a modest effect on QT prolongation. And we don't know, in the context of other medications, what that might mean, again, in a real-world perspective with patients being on numerous medications.

With respect to the 27 milligrams a day, what we heard was that there seemed to be a sense of at least a few members of the panel that the data showed the fact that it was safe for maximum to 27 milligrams a day but not satisfaction that there was 40.

Just lastly with respect to the fact that medications are good if they are decreasing incidence of nausea and vomiting in post-operative situations.

Certainly, one of the patient populations they looked at was a abdominoplasty. And I think I've actually mentioned this before at one of these meetings, but plastic surgeons don't like to see abdominoplasty patients wretch and vomit. They specifically look the anesthesiologist straight in the eye and say, "No nausea, no vomiting."

(Laughter.)

DR. ZACHAROFF: So hopefully I was able to capture the sense. If there's anything I left out, please call it to my attention. If not, we're going to take a 15-minute break and be back at 3:15 sharp to address the two remaining questions, and ultimately take our vote. Thank you.

(Whereupon, at 2:57 p.m., a recess was taken.)

DR. ZACHAROFF: Okay, everyone, welcome back. We're going to proceed to the next discussion question, which we'll see in front of us momentarily. Here we go.

Considering the abuse potential of oliceridine and its proposed use for acute pain in adults for whom an intravenous opioid is warranted, please discuss any

concerns you have regarding the impact of this product, if approved, on public health.

Before we move on to the discussion, I'll just state as per protocol, if there are no questions or comments concerning the word of this question, we'll now open the floor to discussion.

Any concerns about the wording of the question?

(No response.)

DR. ZACHAROFF: Okay. Discussion? Dr. Higgins.

DR. HIGGINS: I guess my concern from a patient perspective is that I don't see any superiority of this medication over another for having abuse deterrence. In comparison to -- the HAP studies that were conducted by the FDA led me to see that there's no difference between morphine in terms of likability and other tests that were done through the HAP study. So I have concerns about the abuse potential.

DR. ZACHAROFF: Thank you. Ms. Phillips?

MS. SHAW PHILLIPS: This really tags on to Dr. Fischer's comments as well, and I think, again,

abuse potential from what we've seen that is like other opioids -- and I agree it should be Scheduled II, but patients or consumers might get the idea it's safer from a respiratory depression standpoint.

So it's definitely not a safer drug to abuse. There's no evidence to show that. And I think it's presumption or word of mouth that it might be safer or could lead to additional abuse or additional risk in the hands of folks that might want to abuse it, but on the whole, not a more abusable substance.

This is getting a little bit off the topic, but I think the other issue in the opioid crisis is drug shortages and drug availability. And I just got another note from my health system saying, "We don't have any PCA syringes that's going out to all the physicians. We've got to manage things other ways," because we can't get enough opioids to treat patients in hospitals because we're trying to decrease the amount of available, and more and more is going to abuse and back channels.

So I think we need to balance having drugs that are effective and able to treat patients with

keeping them out of the hands of those that might abuse them and do themselves ill.

DR. ZACHAROFF: Thank you. Dr. McCann?

DR. McCANN: I agree that the data shows that the drug might be pleasurable much like morphine for a number of patients, but I think it's going to be relatively hard to divert the use of this drug since it's only used in hospitals under supervision, and there's just one formulation.

DR. ZACHAROFF: Thank you. Dr. Goudra?

DR. GOUDRA: Before I say anything, I have couple of clarifications from Trevena. You guys don't recommended it's used during and interoperatively, right? During the procedure?

DR. VIOLIN: No, we have not studied oliceridine interoperatively. In the APOLLO studies and ATHENA, it was started after interoperative anesthetics, including fentanyl and other opioids. So it's never been studied as an interoperative medication.

DR. GOUDRA: Just one more. Have you studied it in terms of intranasal or transmucosal absorption?

DR. VIOLIN: No.

DR. GOUDRA: I know it's [indiscernible] orally?

DR. VIOLIN: Yes. The oral availability is almost zero. We've not --

DR. GOUDRA: And the reason for that?

DR. VIOLIN: First pass effect, so the clearance is fast enough that it's metabolized and just doesn't persist in the body if you take it orally. The only thing we studied is intravenous administration.

DR. GOUDRA: Thank you.

Coming back to my comment, I think the entire dosage is not selective enough, and that's what data seems to say, at 3 times the clinical efficacy does, it loses its selectivity. And as a result, especially because it causes [indiscernible] and it is subective to -- people can seek and use it for abuse purposes. And over and above respiratory depression, we also now have to face the prospect of patients suffering from either hepatic or cardiac toxicity. So I think it is a potential issue.

DR. ZACHAROFF: Thank you. Mr. O'Brien?

MR. O'BRIEN: It seems to me that there -- my concern is it has been expressed in the sense that it's not so much about the drug necessarily. It has the same potential dangers as the other drugs, the other opioids that are out there. It is about the perception in terms of if you know it's going to do this, it's going to do that, it's going to be safer than this other drug. And because of the fact that it's perceived as being safer, that may in fact create a greater danger.

To the comment that it's going to be contained and it's not out for public use, there have been many other drugs that were supposed be contained that are now out in the street for public use. So I'm not quite sure that's something we can hold on to for a long term. So yes, that is a concern that I have, that it may be providing something that's going to create the wrong image in a patient's mind that they can now take the safely when they can't.

DR. ZACHAROFF: Dr. Terman?

DR. TERMAN: Yes. Thank you. So we're back to this question, clearly the abuse potential is

greater than placebo, but the hope is that any new medication is not going to add to the amount of opiates that are being used, but to substitute for other opiates if there's any benefit.

The abuse studies this morning, as you know, I was very interested in that. And it seems like, compared to morphine, that there's either equal or less abuse potential in this drug. I think if there's a public health issue, it's more likely to be what we were just talking about in question 2, which is I have no idea what the dose for PCA is.

I've been writing prescriptions for PCA for 30 years. I have no idea what the maximum amount that FDA thinks we should be using per day of morphine. I don't think that hydromorphone is approved through FDA for PCA, and yet I do that every day. I certainly don't know what the dose is that's approved.

So I think in terms of the indication for -- well, not 0.5 but 0.35 -- and 0.38 might be okay -- that is not the way it's going to -- once we unleash this drug to the population, we are going to see people that are taking a lot more than 24 or

30 milligrams. And the question is, is that something I can live with or others; more importantly, patients can live with.

DR. ZACHAROFF: Okay. Before we summarize this, I will just throw in my own two cents, and that is that I also consider abuse potential of people within the healthcare setting that this drug might be used. We know that people get their hands on drugs that are kept in the hospital, and controlled setting to me means it might be surgicenters or other places where drugs might not necessarily be secured.

In my mind, agreeing with what we heard about maybe the likelihood of equal or less regarding abuse potential, I think that we should assume that many people, this may be considered to be an opioid. And if there's a perception that it's safer, then they might be more likely to go into the drug cabinet and take it out, and give it a whirl, and see what happens.

I think about that from an abuse potential perspective as well as needing to consider risk outside of just the patient and us when we're choosing a certain medication now. We need to consider other

spheres that are moving around, like the community and so on. So I figured I'd just throw that in.

So if there's no further comments for discussion, to summarize, what I got out of hearing your discussion points was that there is no superiority likely for abuse deterrence. Schedule II is probably appropriate for a medication like this. There is concern that people might consider it to be safer to abuse because of things they might hear. Availability, as we heard, is definitely something that drives what people abuse. If it's available, it's going to be abused. And if there's perception that it's an opioid, it's going to be abused.

On the other hand, we heard some thoughts about the fact that it may be less likely to be diverted if it's an institutional setting, but I don't really know what the process will be for wasting a medication like this. I assume it would be what the same process is for wasting any other PCA or syringe with it.

By and large, there was a sentiment that abuse may definitely lead to respiratory depression based on

what we saw with the data, and the increased doses, and the increased likelihood of adverse effects, including possible hepatotoxicity, QT prolongation, and respiratory depression.

If I missed anything you said, please let me know.

(No response.)

DR. ZACHAROFF: No? Okay. Dr. Fischer? Sorry.

DR. FISCHER: There's just one point to add on that from a public health point of view -- and clearly Trevena appropriately asked for this to be Schedule II -- is something to make clear I would think to clinicians, that for those patients we're managing in inpatient settings with a history of opioid use disorders and other problems, I'd be worried that there will be a perception that this is a different kind of opioid, and people will infer that it is somehow safer for patients with that history, which it's not being proposed to say that it is. But when we think about public health concerns, that comes to mind; sort of an outgrowth at the last point you made.

DR. ZACHAROFF: Very good point. So adding to that, the perception is that there might be a perception that this is safer for people who have a history of an opioid use disorder. Thank you.

If there are no further questions or comments, then we will now begin the voting process. The vote is, do you recommend approval of the proposed dose of oliceridine for the proposed indication of the management of moderate to severe acute pain in adults for whom an intravenous opioid is warranted?

After the vote, we'll have the ability to discuss when you're giving us your rationale for the way you voted. If you have feelings about what data might be helpful to gather in the future, you'll have the opportunity to answer that part of the question.

So the vote is that first sentence, do you recommend approval of the proposed dose of oliceridine for the proposed indication of the management of moderate to severe acute pain in adults for whom an intravenous opioid is warranted? Yes?

DR. FISCHER: When you say proposed dose, do you mean both doses that are being proposed or are we

voting separately on each one?

DR. ZACHAROFF: We mean the proposed doses.

DR. FISCHER: Doses.

DR. ZACHAROFF: Yes, doses.

Yes, Mr. O'Brien?

MR. O'BRIEN: Again, I would just like clarification on the question, recommend approval. Now again, we're approving on efficacy and safety, or the ratio of the relationship between efficacy and safety, or -- because the third element is innovation, which is another element, but we're not being asked for innovation. We're being asked for efficacy and safety.

DR. HERTZ: This is Sharon Hertz. To clarify, approval means this goes to market. So based on the available data that you've heard about today, do you think this should be approved for use commercially on the market? However you think about it, I have a regulatory standard for what is necessary, but that's that risk-benefit that I described earlier.

So the question is, should this be approved so that folks can use it in the appropriate setting at the proposed dose?

DR. ZACHAROFF: Dr. Alexander?

DR. HERTZ: For the proposed indication.

DR. ZACHAROFF: Sorry.

DR. ALEXANDER: Just one more point of clarification to follow up on Michael's question about the dose. So we're talking about 1 to 2 milligrams bolus up to a maximum of 40 milligrams a day, with the 2 PCA doses of point 0.1 and 0.35. Correct?

DR. ZACHAROFF: That's correct.

Okay. If there is no further discussion on this, then we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have 20 seconds to vote. Press the button firmly. After you've made your selection, the light may continue to flash. And if you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. ZACHAROFF: Everyone has voted. The vote is now complete. Now that the vote's complete, let's have a look at the vote.

DR. CHOI: For the record, we have 7, yes; 8, no, and zero abstentions.

DR. ZACHAROFF: Now that the vote's complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, state the reason why you voted as you did into the record. And if you feel there's more data necessary, this would be your opportunity to state that as well.

Let's start at this side of the room. Mr. O'Brien?

MR. O'BRIEN: Okay. Well, clearly, I struggled with this to be honest. It is Solomon's sword. I would say that I did it primarily because I think we need something different. We need a new approach. And everything always has its first step, and I see it as a first step.

Now, I say that saying that it's kind of taken within a very small capsule here because I would then want to say an add that we need the appropriate controls. We need the appropriate labeling. We can't let it go out here. I mean, there's an awful lot to define what that means. I do have incredible concern

about a lot of issues here, so I was inclined to say no.

But I also do think that we need to break this epidemic that we have, and I don't think that the approaches that we used so far is in fact going to break it. And we have a community of people that I deal with every day who was stuck between this world where they have no other option than opioids. And we're not giving them a good option. We need a better option.

So thinking of that at the last second, I changed my vote to a yes, and that's the honest truth.

DR. HIGGINS: Jennifer Higgins. I voted no, largely for the reasons that I already mentioned. And with respect to data needed, I will stress again the need for demographic variability. I echo the concerns of other people regarding the safety of the population that was under study and look for people with comorbidities or other kinds of disorders.

Again, I stress the need for older adult research, and I always say that as a gerontologist. But I applaud Trevena for doing some of that with their

studies, but I would like to see more of that. And with respect to the open label, I would have liked to have seen some control data.

DR. WARHOLAK: It's Terri Warholak, and I voted no, although I really do like that this is an innovative molecule and I recognize that better options are needed for pain relief. I was also thinking that specifically in the instances where there are allergies to opioids, this might be a really great option.

So I really struggled with this decision, but it's as stated; it's the proposed doses. And I don't think the dose regimens have a positive risk-benefit profile. I also worry, too, about the perception of the decreased respiratory symptoms. And the reason for that is as it was compared to morphine several times, it wasn't compared in doses that were equivalent. It was stated earlier that the equivalent morphine dose was 5 to 1, and those weren't the doses that were all presented.

So I would really worry that somehow people would get the perception that it is more safe than current opioids, and that might lead to downstream

problems. So for additional data, I would like to see more data mostly on the doses that are proposed and safety, as well as some studies on potential public health risk.

DR. ALEXANDER: This is John Alexander from Duke. I voted yes. Oliceridine is an effective analgesic that probably has improved opioid-related safety. The issue in sorting that out is all about dose equivalency. I do have concerns about off-label use, less about patient population than about regarding dose. I think labeling should include some language about that

The QT risk is probably modest and not unlike a lot of other drugs that are used but has not been completely characterized, and that fact should also be, I believe, described in the label. We definitely need more data, and probably controlled data. I really don't think that single-arm uncontrolled data is going to answer the questions we have in more real-world settings where maybe broader ranges of dosing will be used. And this probably would be a good opportunity to collect additional QT data and further characterize

that QT risk.

DR. TERMAN: Yes. I'm Greg Terman from the University of Washington, Seattle. I voted yes because it'd be nice to have an IV opiate in this country that isn't in short supply. No, I'm kidding.

(Laughter.)

DR. TERMAN: Although I couldn't help the dig.

The issue for me is that the pharmacokinetics of this drug are attractive as someone who does this kind of work full-time. Again, theoretically, for both PK and this arrestin issue should be safer. I'm not convinced that it is, but I am convinced that it's no more dangerous unless it causes dangerous QT changes. And there was nothing that I heard today that convinced me of that. And the open-label trial, as was stated, was all over the place in terms of dosage without dangerous sequelae. So that's the reason I voted yes.

DR. KAYE: Alan Kaye from LSU. I voted no, but it wouldn't have taken that much for me to vote yes. I was concerned about subpopulations. I was concerned about drug-drug interactions. And specifically, in looking throughout the day to try to

understand what we have and how this would be helpful, what I started focusing on was that morphine and dilaudid, which are the principal medications we use post-operatively, don't have associated QT effects.

That is one study, very focused, that would turn me. It was a very difficult vote. Nonetheless, without that information, I wouldn't want to create problems for all the people in our country without that information.

DR. McCANN: Mary Ellen McCann. I also voted no, and actually for precisely the same reasons that Alan Kaye did. I think if this drug's brought up in another half a year or a year with more data, I would be very, very happy to vote yes for this drug. I think it hopefully will be a step forward. I think we just don't have enough safety data to say that we're not going to inadvertently harm people.

DR. SHOBEN: Abby Shoben. I also voted no and sort of echo Dr. McCann's comment about wanting to vote yes and hopefully soon we can because I think it does have a lot of promise as an alternative to morphine in this setting.

I voted no primarily due to this strict interpretation of the question about proposed doses in the 0.1 efficacy versus placebo and if that safety profile is worth it. And I think I would like to see comparison with a more equivalent dose of morphine, as has been said, so that we're not approving a drug that has a less favorable risk-benefit profile to morphine.

DR. ZELTZER: Lonnie Seltzer. I really struggled with this vote. And clearly, as the vote showed, probably a lot of people struggled. The only thing that held me back from a yes vote was I felt like, probably as part of this side of the table, that it's almost ready for prime time but just not quite. And knowing how it will be used in the real world with likely sicker, more complex patients on more drugs, it just needs a little more real-world safety studies, and then I would be much more comfortable knowing how it would be used.

I like the drug. I like the principle behind the drug. It really was a struggle, but that's the last little -- I don't think it will take much, but I think it's just not quite ready yet.

DR. ZACHAROFF: This is Kevin Zacharoff. I voted yes, and I voted yes because I agree with some of the other people who voted yes that this is likely not a more dangerous drug than morphine. I didn't see anything today to indicate maybe that it was better than morphine, but I certainly didn't feel that I saw anything that made it more dangerous than morphine.

The open public hearing actually I found very compelling. Many times in anesthesia, we hear people talk about certain things that work and certain kinds of things that they're doing. We heard the term "off label." I worry that people might use a medication like this in an off-label way, but the reality is that people do and try, and we anesthesiologists do and try all the time.

I didn't feel that it was superior to morphine other than the fact that at least there was a possible chance that in some patient populations, the adverse effect profile might actually be lower.

DR. LITMAN: Ron Litman. I voted yes because I asked myself what if there were no opioids, and this was the first in class, would I want this for myself?

And the answer is yes, of course. That being said, I do agree with everybody else on the panel, even those that voted no.

The question then becomes, how much more data do we need? And it would be wonderful to have just a little bit more, as Dr. Zeltzer said, but thinking about historically and other drugs, that kind of data is rarely available. And the truth is that what we agreed to or approve for labeling on the dose is not real life as we talked about.

Whether we like it or not, the reality is that most prescribers won't read the label, and it's legal to do so. And once it's marketed, it's legal to use it however we want, and that occurs. What's not legal is for the company to market it for non-truthful purposes. So I wonder if the FDA could ask for some kind of language in the labeling that states something about this drug has not been shown to be safer than morphine or safer than traditional opioids until the truth of that comes out.

So then in the end, I had to ask myself, as a representative of the American people, is it better to

let them benefit from a drug that could possibly be better, or do I withhold it from the American people until we know that it's safe enough for them to use? And in the end, I came down to the former.

I think that these kinds of issues work themselves in phase 4 studies, in non-sponsored studies over the years. As Dr. Terman alluded to before, we take a chance, and it's something we grapple with if we unleash this drug too early by mistake. But there's no way we can know that today. There just isn't.

So overall, I had to look at their overall safety profile on a couple thousand of patients that have been exposed to it, the ones we knew about, and I tended to vote yes.

DR. GOUDRA: Dr. Goudra from Penn medicine. I did vote yes for many reasons. One, it doesn't interact in metabolites, and I think that's a good thing. You can use it in patients with renal failure, where we can't use morphine for example.

It doesn't cause histamine release [ph]; that's good. I view every opioid as abuse problem, so it's no exception. And yes, 0.1 is a problem or 0.35.

As Dr. Litman pointed out, we will figure out how to use it once it is in the market. And drug interactions, knowing almost 80 percent of the drug undergoes hepatic microsomal enzyme metabolism. We deal with that all the time. Long QT interval, everybody gets Zofran almost, so that doesn't seem to be a problem considering there are so many drugs for long QT, which we use.

Yet, we do need much more selective G-protein or something which doesn't have any beta arrestin pathway activation. But I think it's a good beginning and not having anything to kill this product at this stage. Thank you.

DR. FISCHER: Mike Fischer from Boston. I voted no. And many of the reasons have been said, so I'll recap briefly. I agreed with many of the points by the group around that corner of the table, who are generally in agreement, concern about the lack of difference from placebo of the lower dose and some of the subpopulations, where the drug is likely to see its highest use.

Then going to a couple of the points that were

made at the end to highlight the difference, like my colleagues here, it was a tough decision. It feels like it is very, very close. But I was given pause by the disconnect from the overall theme. And actually, Kevin, I took some of the comments a little differently.

I felt like the theme that was coming out overall was that here is a drug that is going to be the answer to what we've been looking for. Here is something that's much better. And when I went back and took -- when I'm taking a hard look at the data, what I think we have so far for the doses that are being requested is something that is a little less effective and a little safer. And that's not the message that is coming across pretty strongly.

I take Dr. Litman's point that if there were nothing available, perhaps this would be -- and we needed something. But given how this is likely to be used and the fact that phase 4 studies take a long time and are hard to do, that disconnect gave me pause.

I feel like this is very, very close. If we can get safety data at the doses at which this is

actually likely to be used, I think that would be reassuring. And as one of the other panelists said, it feels like it wouldn't need to be a very long time to accumulate enough data to have us be reassured enough that it's a safe alternative but also to release it out there into the wild with a clear message about where the relative safety and efficacy are.

MS. SHAW PHILLIPS: Marjorie Shaw Phillips. I voted yes, the same kind of thing. I thought it was better to vote yes with some qualifications rather than no with some qualifications because I think it's important that drugs in this class get on the market, and there are some important benefits.

I think the important thing is safety or relative safely at effective doses. And for individual patients, it looks like it will totally be worth it because we're really not talking about equivalent doses. We're talking about doses that will meet individual patient's needs.

The PK profile, the lack of active metabolites, the relative safety at the steady state at the proposed PCA doses and proposed bolus doses all

look good and are positive; the potential for less GI side effects at those proposed doses as well. If I were going to qualify it, one of the things I would like to see is a statement that has not been adequately studied at doses greater than 27 milligrams a day and would be an opportunity to do that.

As far as further studies, I think looking at it in opioid-tolerant patients and those that would have higher opioid demands would be useful information. And again, with the additional information in phase 3, it would be worth the trade off for not getting an important drug to market.

I do think also, as mentioned earlier by our pharmacist colleague, that having an alternative for patients who have morphine-related allergy or severe side effects and tolerances is also important.

DR. SOLGA: Steve Solga. I voted no. Unlike some others, I actually felt fairly firm with my no. I felt like the efficacy versus placebo is there, but the overall risk-benefit consideration to me was not. Three doses of study drug were compared to a single dose of morphine. If there was slightly less morphine

provided, I think all of the differences would go away, and you'd basically have a me-too of a lower dose of morphine, which does not meet the urgent unmet need and is not innovative. In fact, it would potentially be the opposite.

So I just want to be excited about these data, but I found myself unable to be so.

In terms of what to do for a follow-up study, I also found the public comments to be very important. Many persons said they felt more awake. They were talking. They were eating. They were moving. They were engaged with their family. They moved their bowels.

The summation of all of that means discharge. So maybe a trial could be done, a randomized-controlled trial, comparing time to discharge for a standard operation where length of stay might be expected to be 24 hours. That could be an amalgam of both safety and efficacy if study drug got folks out the door at 20 hours and morphine got them out the door at 30 hours, and ding, ding, ding, ding.

I get that idea from some years ago when FDA

looked at maintenance of remission of hepatic encephalopathy with rifaxmin, encephalopathy endpoints were simply too unreliable to study. There was no good way to do that. So what FDA and sponsor agreed on was rather than looking at encephalopathy endpoints, they would simply look at time to readmission to the hospital, time to readmission; very firm, very simple. This could simply be the opposite, time to discharge.

DR. ZACHAROFF: Well, I want to thank you very much for your good work today. Before we adjourn, I'm just going to ask if there are any last comments from the FDA.

DR. HERTZ: I'm not sure you made our job any easier --

(Laughter.)

DR. HERTZ: -- but I think that you gave us a lot to think about, and I appreciate the work you've done today. Thank you.

Adjournment

DR. ZACHAROFF: Panel members, please take all your personal belongings with you as this room is cleaned at the end of each meeting day. Any materials

left on the table will be disposed of. Please also remember to drop off your name badge at the registration table on your way out so they may be recycled, and we will now adjourn the meeting formally. Thank you very much.

(Whereupon, at 3:54 p.m., the meeting was adjourned.)