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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

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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

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

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

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

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

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

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

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

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

22 DR. LITMAN: Ron Litman, pediatric

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

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

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

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

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

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

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

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

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

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

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

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

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

20 DR. ZACHAROFF: Thank you.

21 For such topics as those being discussed at
22 today's meeting, there are a variety of opinions, some

1 of which are quite strongly held. Our goal is that
2 today's meeting will be a fair and open forum for
3 discussion of these issues and that individuals can
4 express their views without interruption. Thus, as a
5 gentle reminder, individuals will be allowed to speak
6 into the record only if recognized by the chair. We
7 look forward to a productive meeting.

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

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

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

Conflict of Interest Statement

1
2 DR. CHOI: The Food and Drug Administration is
3 convening today's meeting of the Anesthetic and
4 Analgesic Drug Products Advisory Committee under the
5 authority of the Federal Advisory Committee Act of
6 1972. With the exception of the industry
7 representative, all members and temporary voting
8 members of the committee are special government
9 employees or regular federal employees from other
10 agencies and are subject to federal conflict of
11 interest laws and regulations.

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

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

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

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

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

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

4 This is a particular matters meeting during
5 which specific matters related to Trevena's NDA will be
6 discussed. Based on the agenda for today's meeting and
7 all financial interests reported by the committee
8 members and temporary voting members, no conflict of
9 interest waivers have been issued in connection with
10 this meeting. To ensure transparency, we encourage all
11 standing committee members and temporary voting members
12 to disclose any public statements that they have made
13 concerning the product at issue

14 With respect to the FDA's invited industry
15 representative, we will like to disclose that
16 Dr. William Herring is participating in this meeting as
17 a nonvoting industry representative, acting on behalf
18 of regulated industry. Dr. Herring's role at this
19 meeting is to represent industry in general and not any
20 particular company. Dr. Herring is employed by Merck &
21 Company.

22 We would like to remind members and temporary

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

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

12 **FDA Opening Remarks - Sharon Hertz**

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

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

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

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

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

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

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

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

10 DR. ZACHAROFF: Thank you, Dr. Hertz.

11 Before we begin the applicant presentations,
12 it's important to note that both the Food and Drug
13 Administration and the public believe in a transparent
14 process for information-gathering and decision-making.
15 To ensure such transparency at the advisory committee
16 meeting, FDA believes that it is important to
17 understand the context of an individual's presentation.

18 For this reason, FDA encourages all
19 participants, including the applicant's nonemployee
20 presenters, to advise the committee of any financial
21 relationships they may have with the applicant, such as
22 consulting fees, travel expenses, honoraria, and

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

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

9 We will now proceed with Trevena's applicant
10 presentations.

11 **Applicant Presentation - Maxine Gowen**

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

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

1 new molecule in this class of drugs in decades.

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

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

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

21 When an agonist like morphine binds to the mu
22 opioid receptor, it stabilizes receptor conformations

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

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

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

1 not a derivative of opium such as morphine or
2 hydromorphone.

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

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

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

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

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

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

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

22 We don't expect the approval of IV oliceridine

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

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

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

1 we set out to study respiratory safety using several
2 approaches.

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

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

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

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

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

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

19 Based on our learnings and results from the
20 clinical studies, our proposed dosing is as follows.
21 Every patient should get an initial bolus dose of 1 to
22 2 milligrams. Subsequent doses may be given

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

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

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

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

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

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

11 **Applicant Presentation - Mark Demitrack**

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

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

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

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

13 Patients on placebo experienced little to no
14 pain relief. Patients in the morphine 4-milligram
15 group had significantly lower pain scores than placebo
16 with an approximate 2-point change from baseline. The
17 oliceridine 0.5 and 1-milligram groups had reductions
18 in pain that were similar to morphine. The oliceridine
19 2- and 3-milligram groups had greater reductions in a
20 dose-dependent manner, providing 5 to 6-point mean
21 reductions by 5 minutes after dosing.

22 What this tells us is as you increase the dose

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 Compared to morphine, in both studies, the
11 treatment responder rate was lower for the
12 0.1-milligram regimen. The 0.35- and 0.5-milligram
13 regimens had responder rates that were not
14 significantly different from morphine.

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

1 additional support for the conclusion that the
2 0.5-milligram regimen does not meaningfully increase
3 efficacy beyond the 0.35-milligram regimen.

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

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

1 minimize opioid exposure.

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

8 For the SPID analysis, rescue medication use
9 is imputed using last observation carried forward for
10 the duration of the labeled dosing interval.

11 Discontinuation of study medication for any reason,
12 which we view as an important indicator of patient
13 comfort, is not accounted for. Discontinuation for
14 lack of efficacy is also handled with LOCF imputation,
15 and discontinuation for an adverse event is handled
16 using baseline observation carried forward imputation.

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

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

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

9 On this slide, I'd like to kind contrast the
10 responder and SPID analyses and how they help to
11 clarify why this conclusion makes clinical sense. When
12 looking at SPID LOCF analysis or the magnitude,
13 0.5-milligram regimen looks about twice as efficacious
14 as the 0.35-milligram regimen. However, when we look
15 at the treatment responder rate, the use of rescue
16 analgesia, discontinuation for lack of efficacy,
17 patient dissatisfaction, and clinician dissatisfaction,
18 the 0.35 and 0.5 regimens are virtually identical.
19 Similar findings were observed in APOLLO 2.

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

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

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

13 When we look at the difference between the
14 point 0.35-milligram oliceridine and morphine regimens,
15 shown in the yellow highlighting, we see that after
16 3 hours, morphine separates from oliceridine by about 1
17 to 1 and a half points. The FDA briefing document
18 notes that this suggests morphine is more efficacious
19 than the oliceridine 0.35-milligram regimen. However,
20 when we look at the incidence of rescue medication of
21 each regimen over 12 hours, as shown on the right of
22 the slide, there was no difference between oliceridine

1 and morphine.

2 Therefore, the separation of the
3 0.35-milligram in morphine regimen in pain scores does
4 not appear to reflect any additional magnitude of
5 analgesia without any apparent clinically meaningful
6 benefit since patients found the sufficiency of
7 analgesia the same. The higher magnitude of efficacy
8 with morphine may be related to the delayed onset of
9 accumulating active metabolites. Similar findings were
10 observed in the APOLLO 2 study.

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

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

1 approval.

2 After an initial loading or bolus dose of 1 to
3 2 milligrams, analgesia can be maintained with a range
4 of on-demand doses, 0.1 milligram being the lowest
5 efficacious demand dose and 0.35 providing maximum
6 efficacy. In clinical practice, physicians can select
7 the demand dose that is most appropriate for the
8 patient based on the severity of pain and the patient's
9 response, and titrate within that range as appropriate.

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

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

1 sequelae.

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

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

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

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

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

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

1 safety.

2 Dr. Watkins?

3 **Applicant Presentation - Paul Watkins**

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

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

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

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

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

14 In this graph of the 252 patients who received
15 placebo in the phase 2 and 3 studies, you can see in
16 the right-lower quadrant of the graph that there are 4
17 who experienced elevations in serum
18 ALT exceeding 3 times the upper limit of normal,
19 1.6 percent of the population, indicating that there's
20 a background of liver injuries in this patient
21 population.

22 With morphine, you can see that there were

1 5 patients who experienced an elevation in serum ALT
2 exceeding 3 times the upper limit of normal, also about
3 1.6 percent, again pointing to the background incidence
4 of liver injuries in this patient population.

5 With oliceridine, there are more individuals
6 in the right-lower quadrant, but this represents a
7 similar percentage of the patient population,
8 2.2 percent, which is not statistically different from
9 what was observed during treatment with morphine and
10 placebo.

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

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

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

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

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

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

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

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

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

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

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

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

7 **Applicant Presentation - Robert Kleiman**

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

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

22 A comprehensive battery of preclinical cardiac

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

10 The two metabolites have absolutely no effect
11 on hERG or other cardiac ion channels. For
12 oliceridine, the hERG IC50 is 4.3 micromolar, which is
13 116 times greater than the maximum human exposure.
14 Furthermore, there was no QT effect in the isolated
15 rabbit wedge preparation or in cynomolgus monkeys at an
16 oliceridine exposure 8-fold than the maximum human
17 exposure.

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

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

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

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

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

1 clinically significant effect on QTc, and the
2 6-milligram suprathapeutic dose shown by the Blue
3 line produced slight QT prolongation. The mean Cmax
4 for the 6-milligram dose was 284 nanograms per
5 milliliter, which is 3 times greater than the average
6 Cmax in clinical use.

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

15 The FDA recommended obtaining ECGs in phase 3
16 at baseline following the first dose, and then
17 periodically at later time points to look for potential
18 delayed effects on QTc. Trevena followed these
19 recommendations by collecting ECGs in more than
20 1500 patients in phase 3 at baseline, after 1 hour to
21 study acute effects, and every 24 hours to detect any
22 potential delayed effect due to metabolite accumulation

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

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

11 By 24 hours, oliceridine and its metabolites
12 are at or near steady-state levels. Therefore, the ECG
13 collection at 24 hours was sufficient to detect any
14 potential delayed QTc effects with repeat dosing. And
15 here are the ECG results from the controlled phase
16 3 APOLLO studies. There were no meaningful differences
17 in the incidence of clinically significant QT
18 prolongation across any of the oliceridine, morphine,
19 or placebo groups.

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

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

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

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

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

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

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

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

19 **Applicant Presentation - Jonathan Violin**

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

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

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

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

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

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

16 We evaluated analgesia on respiratory effects
17 using a randomized, double-blind, placebo-controlled
18 crossover design. Thirty healthy volunteers were
19 randomized and received study drug. As a crossover
20 study, all volunteers participated in each of the
21 5 periods in a random order: placebo, a high
22 10-milligram dose of morphine, and oliceridine 1.5, 3,

1 and 4.5 milligrams as 2-minute Iv infusions.

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

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

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

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

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

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

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

22 We sought to explore the impact of this effect

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

9 As you heard earlier, the oliceridine regimens
10 had analgesic efficacy equivalent to morphine. In that
11 context, we observed significantly fewer
12 hyperventilation events with oliceridine than morphine.
13 The risk of a hyperventilation event was 71 percent
14 lower for the oliceridine 0.1-milligram regimen and
15 42 percent lower with the 0.35-milligram regimen.

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

1 severity, and duration of the relevant clinical events.

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

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

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

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

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

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

1 ensuing displays, we're only focusing on the range of
2 on-demand doses we are proposing for approval, 0.1 and
3 0.35 milligrams.

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

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

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

1 0.1 milligram regimen and 36 percent lower for the
2 0.35-milligram regimen. For vomiting, the incidence
3 was 64 percent lower than morphine for both oliceridine
4 regimens.

5 Phase 3 results were consistent with the
6 phase 2b study. The incidence of nausea was
7 significantly lower in the 0.1-milligram regimen
8 compared to morphine, and the incidence of vomiting was
9 significantly lower for both the 0.1 and 0.35 regimens,
10 41 to 61 percent lower than morphine.

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

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

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

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

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

1 olliceridine reduced opioid-induced respiratory
2 depression by about 50 percent compared to
3 equianalgesic doses of morphine.

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

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

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

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

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

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

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

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

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

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

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

1 provide his clinical interpretation of the results.

2 **Applicant Presentation - Gregory Hammer**

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

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

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

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

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

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

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

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

9 In the phase 2b study, 3 and 4 patients
10 receiving morphine had nausea. Oliceridine reduced the
11 incidence by 35 to 40 percent; 2 and 5 morphine
12 patients vomited, which oliceridine reduced risk by 64
13 percent. In the phase 3 studies, 2 and 3 morphine
14 patients experienced nausea, and oliceridine reduced
15 the incidence by 15 to 40 percent. 1 and 2 patients
16 taking morphine vomited, which oliceridine reduced by
17 40 to 60 percent.

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

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

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

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

22 The ventilatory response to hypercapnia test

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

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

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

1 patients had a respiratory safety event.

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

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

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

1 procedure was relatively minor.

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

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

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

1 eliminate adverse events altogether or reduce drug
2 liking.

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

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

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

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

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

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

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

13 In terms of respiratory safety, certainly
14 there's no greater safety risk with oliceridine than
15 morphine. Rather, every endpoint we've measured
16 throughout development is either numerically or
17 statistically better than morphine. Definitively
18 proving a safety benefit was never contemplated as an
19 approval requirement. Nevertheless, we're encouraged
20 by the uniformly consistent relative risk reductions
21 for opioid-induced respiratory depression in the phase
22 1, phase 2, and phase 3 studies compared to morphine.

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

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

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

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

1 Secondly, the olliceridine safety and tolerability
2 profile represents an incremental but important
3 improvement over conventional IV opioids.

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

6 **Clarifying Questions**

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

12 Dr. Goudra?

13 DR. GOUDRA: Dr. Goudra from Penn medicine.
14 Too many questions, but I'm going to ask all of them.
15 In reference to slide 33, could it be ceiling effect in
16 terms of better efficacy at higher doses at 0.5 versus
17 0.35? I know it's not clinically significant in terms
18 of QT prolongation or death -- sorry; not significant
19 at clinical doses, but could it be a problem in toxic
20 doses like tricyclics?

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

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

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

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

10 With respect to a ceiling effect for efficacy,
11 no, we don't think there's a ceiling effect. In fact,
12 when we give patients higher doses of oliceridine as we
13 did in phase 2 bunionectomy study -- in fact, let's
14 bring up the core slide for the first dose in study
15 2001, please.

16 What we see is that when we get up to doses of
17 2 and 3 milligrams of oliceridine, patients can go from
18 a 7 out of 10 pain score, so severe pain, to an average
19 of 1 in 5 minutes. Certainly it's higher than the
20 4-milligram dose of morphine, but that's the sign of a
21 very powerful analgesic.

22 So the key thing to remember in the phase 3

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

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

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

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

1 clinically significant.

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

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

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

17 DR. KLEIMAN: That's a good question. In
18 general, when you have a drug that has a greater than
19 20-milliseconds QTc increase, you would expect to want
20 to mitigate its effects by limiting concomitant use
21 with other QT prolonging drugs or in long
22 QT syndrome.

1 For a drug with an negligible but just above
2 10-millisecond upper confidence bound, I think I would
3 probably worry about using it in some with congenital
4 long QT syndrome just because we don't know how a
5 particular individual with a genetic susceptibility
6 would respond. I don't have any particular concerns in
7 the case of the approved drugs such as ondansetron,
8 that also have modest QT prolongation effects.

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

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

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

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

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

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

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

8 DR. GOUDRA: Thank you.

9 DR. ZACHAROFF: Dr. Litman?

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

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

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

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

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

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

16 DR. LITMAN: Right.

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

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

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

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

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

17 DR. LITMAN: So speaking of which, can you
18 pull up slide CO-20 again? It's a very impressive
19 slide on the surface. And I wanted to ask, when you
20 started giving higher doses of oliceridine and you got
21 better pain control, were those equally potent to
22 4 milligrams of morphine, those doses?

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

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

11 DR. VIOLIN: Sure. Again, this was a
12 fixed-dose study. We wanted to study PRN in phase 3,
13 but let's look at the phase 1 study, looking at
14 analgesia. There we looked at a 10-milligram dose of
15 morphine. We wanted to go as high as we thought we
16 could in our first-time-in-human study. Here, compared
17 to a 10-milligram dose of morphine in this pain model,
18 we were able to match or at least numerically beat that
19 10-milligram dose with 3 and 4 and a half milligrams of
20 oliceridine.

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

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

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

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

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

22 DR. VIOLIN: Sure. The principal investigator

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

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

7 So your question is?

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

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

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

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

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

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

10 (Laughter.)

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

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

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

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

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

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

11 DR. WEBSTER: Yes.

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

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

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

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

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

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

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

3 DR. LITMAN: And the same thing with cardiac.

4 DR. VIOLIN: Correct.

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

9 DR. VIOLIN: Of oliceridine?

10 DR. LITMAN: Yes.

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

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

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

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

10 What was the other question? Sorry.

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

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

19 DR. LITMAN: Thanks for indulging all my
20 questions.

21 DR. ZACHAROFF: Thank you. Dr. McCann?

22 DR. McCANN: Thank you. Dr. McCann from

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

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

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

22 In the ATHENA study, again, that was care as

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

6 DR. KLEIMAN: You raise an excellent point.
7 What happens to patients who are already taking QT
8 prolonging meds or are going to get ondansetron, which
9 is going to happen obviously. But if you take a look
10 at what happens with the therapeutic, the top-range,
11 single therapeutic dose of 3 milligrams, the mean Cmax
12 152 nanograms per milliliter, about 50 percent higher
13 than the mean Cmax with clinical use, they don't have a
14 significant QT effect. So adding ondansetron to that
15 is not going to produce a problem.

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

21 Now, that covers the parent. That covers the
22 suprathreshold exposure of oliceridine. How about

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

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

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

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

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

4 DR. ZACHAROFF: Thank you. Dr. Zeltzer?

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

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

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

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

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

9 DR. ZACHAROFF: Dr. Higgins?

10 DR. HIGGINS: Jennifer Higgins. My question
11 is more about demographics. I was struck by the APOLLO
12 studies and the lack of men in those studies. And I'm
13 wondering why there were so few. Page 43 of the
14 background materials says that the 3002 study had only
15 3 men, whereas you had 398 females. I'm wondering how
16 this would impact dosing, and I'm wondering if you did
17 any gender comparative analyses.

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

1 oliceridine, but it's a small number.

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

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

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

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

5 DR. ZACHAROFF: Dr. Solga?

6 DR. SOLGA: Steve Solga from Penn.

7 Dr. Violin, I'm just looking for some clarification and
8 some help. I read through both briefing packets quite
9 carefully, but I'm still trying to understand the
10 hypothesis and how it adapts to clinical data.

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

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

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

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

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

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

1 essentially putting the brakes on the analgesic
2 signaling.

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

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

12 DR. VIOLIN: No. Yes, and that's a challenge
13 when trying to run these kinds of studies. In terms of
14 what comparator should we use, we really wanted to
15 focus on a clinically relevant morphine dose, something
16 that's widely used, the 4-milligram loading dose; the
17 1-milligram on demand; 6-minute lockout. Certainly
18 there are alternatives. There's an infinite
19 combination of parameters you could use for morphine
20 PCA. We wanted something that would be a very
21 reasonable benchmark, and we wanted to be consistent
22 across studies.

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

5 This I think gets to one of the questions
6 related to magnitude versus sufficiency of efficacy,
7 given the SPID analysis suggests that the
8 0.35-milligram dose really isn't doing the job that
9 morphine can do. But then when we look at
10 discontinuations, at patient satisfaction, at rescue
11 use, it's really comparable.

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

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

22 Would there be any reason to expect it would

1 be less efficacious with this drug?

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

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

15 DR. ZACHAROFF: Thank you. Dr. Terman?

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

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

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

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

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

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

1 4 and a half milligram oliceridine dose markedly
2 outperformed the 4-milligram morphine. From hours 2 to
3 4, they're pretty similar.

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

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

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

20 DR. VIOLIN: Ten minutes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

19 DR. ZACHAROFF: Thank you. Dr. Alexander?

20 DR. ALEXANDER: Thank you. John Alexander.

21 I'm from Duke. My first questions are for Dr. Kleiman,
22 and the first one's really simple. Who interpreted the

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

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

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

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

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

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

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

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

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

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

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

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

11 DR. ALEXANDER: Okay. Then just one last
12 question. If I look at the proposed dosing regimen,
13 which is an initial bolus of 1 to 2, and then
14 subsequent boluses of 1 to 2 milligrams every
15 10 minutes -- so I don't treat pain professionally, but
16 I can see people getting a lot more than 6 milligrams
17 in an hour.

18 In the range of patients who would get this
19 drug clinically for the wide range of pain syndromes,
20 acute pain syndromes that they'd be getting it, what do
21 you think the maximal doses would be in 1, 3, or
22 6 hours? We know that in 24 hours it's 40 milligrams,

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

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

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

16 DR. ALEXANDER: Thank you.

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

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

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

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

10 DR. ZACHAROFF: Okay. That was my question.

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

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

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

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

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

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

22 DR. ZACHAROFF: Thank you.

1 Mr. O'Brien?

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

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

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

1 That being said, I have three questions, I
2 guess, that I'd like to ask of Dr. Hammer,
3 Dr. Demitrack, and Dr. Violin. First with Dr. Hammer,
4 if I could just ask you, in terms of dosage, I was on
5 40 milligrams of oxycodone prior to the surgery,
6 11 months prior to the surgery. I was also diagnosed
7 with sleep apnea.

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

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

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

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

7 MR. O'BRIEN: Thank you.

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

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

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

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

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

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

15 DR. VIOLIN: Sure. Here we go.

16 MR. O'BRIEN: On the patient view, if I
17 understand it, going from point 0.35 to .05 terms of
18 satisfaction, the highest satisfaction is with 0.5.
19 But you're not asking for 0.5, so now you go to point
20 0.35, which is actually less than the morphine.

21 Is that the way I read that slide?

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

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

6 MR. O'BRIEN: Okay.

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

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

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

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

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

9 DR. VIOLIN: You're correct. The adverse
10 events tend to be a little more higher incidence with
11 point 0.5 milligram compared to 0.35-milligram regimen.
12 That's why we're not proposing approval for 0.5 because
13 when we look at these measures that we think are linked
14 to patient comfort, or adequacy, or sufficiency of pain
15 relief, there's no real benefit of 0.5 above and beyond
16 0.35.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 DR. ZACHAROFF: Thank you.

7 MR. O'BRIEN: Thank you very much.

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

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

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

1 before.

2 Dr. Kilgore?

3 DR KILGORE: Yes. Good morning.

4 Dr. Elizabeth Kilgore, medical officer, FDA.

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

7 **FDA Presentation - Elizabeth Kilgore**

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

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

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

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

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

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

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

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

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

21 **FDA Presentation - Katherine Bonson**

22 DR. BONSON: Good morning. My name is

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

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

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

1 equivalent to or greater than human therapeutic plasma
2 levels.

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

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

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

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

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

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

1 pathway.

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

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

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

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

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

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

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

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

7 In the study that they conducted with
8 oliceridine, rats were trained to discriminate morphine
9 from vehicle, and then morphine was tested over a range
10 of doses, and as expected, it produced full
11 generalization to itself when the morphine cue was
12 tested. And oliceridine over a range of doses also
13 produced full generalization at the higher doses, 75 to
14 99 percent. These data suggest that oliceridine
15 produces sensations that are similar to morphine, and
16 this was expected of course because oliceridine is a mu
17 opioid agonist like morphine.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 that are asked about, but of interest to us are the
2 ones that are related to opioids. Both oliceridine and
3 morphine were identified as morphine or oxycodone, and
4 the range was very similar, 72 to 84 for oliceridine;
5 88 to 99 for morphine. They were also identified as
6 codeine and heroin with somewhat less scores. So
7 oliceridine was consistently identified as one of
8 several opioids familiar to drug abusers.

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

14 Somnolence was also reported at a high rate
15 for both, 8 to 20 from oliceridine and 15 to 33 percent
16 for morphine. Parasthesia was also frequently reported
17 for oliceridine, 3 to 8 percent, and for morphine, 8 to
18 19 percent, but placebo did not produce any reports of
19 these adverse events.

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

1 high, good drug effects, and take drug again that were
2 far outside of the acceptable placebo range.

3 Oliceridine was also identified as an opioid and
4 produced adverse events that included a high rate of
5 euphoric effects.

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

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

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

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

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

5 **FDA Presentation - James Travis**

6 DR. TRAVIS: Thank you, Dr. Bonson.

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

17 The applicant conducted two efficacy studies,
18 3001 in patients undergoing bunionectomy, and 3002 in
19 patients undergoing abdominoplasty. The overall design
20 of these studies were similar with a few notable
21 differences, including the duration of the study
22 period, which is 48 hours for 3001 and 24 hours for

1 3002.

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

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

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

22 The applicant included one safety endpoint,

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

10 Here is the dosing schedule used in both
11 studies. Patients were randomized to 1 of 5 treatment
12 arms: placebo, morphine, or one of 3 oliceridine
13 treatment arms. Patients received an initial loading
14 dose, which was either 1.5 milligrams of oliceridine,
15 4 milligrams of morphine, or matched placebo. Patients
16 then received demand doses via PCA pump with a 6-minute
17 lockout interval.

18 The 3 oliceridine treatment arms each received
19 different demand doses with demand doses set at .01,
20 0.35, or 0.5 milligrams. The morphine treatment arm
21 demand doses were set at 1 milligram. Patients could
22 receive additional clinician-administered supplemental

1 doses, at most, 1 per hour.

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

9 I will now present the efficacy analysis. The
10 applicant analyzed the response rates using a logistic
11 regression model, which included treatment group as a
12 fixed factor with baseline pain score and study site as
13 covariates. To adjust for multiplicity, the applicant
14 used Hochberg adjustment to control the overall type 1
15 error. Simply put, if the largest p-value was greater
16 than 0.5, then the next largest p-value was tested at
17 0.025. If this p-value was not less than 0.025, then
18 the last value was tested at 0.167.

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

1 rescue medication included.

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

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

12 One issue with the response definition is that
13 it truncates the improvements in SPID score to either
14 less than 30 percent or greater than 30 percent,
15 turning a continuous measure into a pass/fail.

16 Patients who experienced a 30 percent reduction are
17 treated exactly the same as patients who experienced
18 much greater pain relief. This causes the difference
19 between oliceridine and morphine to be understated.

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

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

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

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

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

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

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

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

14 All 3 doses of oliceridine provided
15 statistically significantly greater pain relief than
16 placebo. In contrast to the applicant's analyses where
17 there were no differences, there are now statistically
18 significant differences between morphine and the
19 3 doses of oliceridine in this study.

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

1 compared to placebo and again found response rates
2 within 5 percent of morphine for oliceridine
3 0.35 milligrams and 0.5 milligrams. This time,
4 however, the odds ratio response for oliceridine
5 0.1 milligrams and morphine was statistically
6 significant.

7 Using the same methodology presented for study
8 3001, we obtained this figure, with the X-axis, again,
9 showing the time since the initial loading dose and the
10 Y-axis showing the average pain intensity at each time
11 point for each study arm.

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

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

1 0.5-milligram doses of oliceridine.

2 Morphine was superior to the 0.1- and
3 0.35-milligram oliceridine doses, and though not
4 statistically significant, the SPID scores for the
5 oliceridine 0.5-milligram group were lower than the
6 morphine treatment group.

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

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

1 population.

2 The objective of this analysis was to evaluate
3 whether there was a clinically meaningful benefit in
4 respiratory safety for oliceridine over morphine.

5 There were several issues with these analyses. First,
6 FDA does not agree with how this endpoint was defined
7 as it is subjectively defined based on the
8 investigator's discretion, which makes it difficult to
9 interpret.

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

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

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

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

3 The observed in the model-estimated cumulative
4 duration of safety events both exhibit a clear dose
5 response relationship for oliceridine. And while the
6 p-value for the 0.1-milligram dose is less than 0.5, it
7 is not considered statistically significant because of
8 the Hochberg adjustment for multiplicity. The
9 model-estimated respiratory safety burden, seen in the
10 third row, was 15 minutes for oliceridine compared to
11 33 minutes for morphine for a difference of 18 minutes.

12 For the abdominoplasty study 3002, we again
13 see no statistically significant differences for any
14 oliceridine dose compared to morphine. The oliceridine
15 0.1-milligram dose was again not significant after
16 adjusting for multiplicity. For this study, the
17 estimated difference in duration of respiratory safety
18 events between oliceridine 0.5 and morphine was about
19 5 minutes compared to 18 minutes for the previous
20 study.

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

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

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

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

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

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

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

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

1 placebo.

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

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

15 While the highest dose of oliceridine
16 0.5 milligrams has significantly lower efficacy
17 compared to morphine, opioid-related adverse event
18 rates are similar.

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

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

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

12 **FDA Presentation - Elizabeth Kilgore**

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

20 For dosing, Dr. Travis has described the phase
21 3 double-blind studies and dosing in those studies. In
22 study 3003, a phase 3 open-label study in surgical and

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

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

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

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

1 for the label a number of times. Currently, the
2 applicant proposes a maximum daily dose of
3 40 milligrams and a PCA demand dose of 0.1 and 0.35
4 milligrams.

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

11 In prior advice, the applicant was advised of
12 a required exposure for at least 350 patients at the
13 highest plan dose. The applicant initially proposed
14 100 milligrams daily, shown on the far-right arrow, but
15 few patients were exposed. They now propose the 40
16 milligrams daily, shown on the middle arrow, but
17 exposure still does not meet the required safety
18 database. The highest dose that at least 350 patients
19 were exposed to during the first 24 hours was 27
20 milligrams of oliceridine shown at the first arrow.

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

1 smaller than the agency's recommended to evaluate and
2 support the safety of oliceridine for the proposed
3 label. The highest dose with the longest actual
4 duration that had at least 350 patients exposed was
5 37.2 milligrams, administered over a natural duration
6 of at least 34.5 hours.

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

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

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

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

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

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

1 The percentage of discontinuations due to
2 adverse events was higher for oliceridine 0.35
3 milligrams and 0.5 milligrams compared to morphine in
4 study 3002. There were no adverse events leading to
5 discontinuation in the placebo or oliceridine
6 0.1-milligram treatment groups. As shown, the types of
7 adverse events leading to discontinuation in
8 oliceridine were primarily opioid related.

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

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

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

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

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

22 Next, I will discuss specific safety

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

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

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

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

1 event with markedly elevated transaminase levels.

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

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

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

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

1 medications.

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

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

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

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

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

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

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

18 The applicant's thorough QT study assessed the
19 effect of oliceridine on the QTc interval at 3 and
20 6 milligrams. Results showed a dose-proportional
21 increase in QTc at approximately 1 hour after time of
22 peak plasma concentration. There are a number of

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

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

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

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

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

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

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

19 **Clarifying Questions**

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

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

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

11 DR. HIGGINS: No.

12 DR. ZACHAROFF: Dr. McCann?

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

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

1 scientific.

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

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

8 DR. McCANN: Yes.

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

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

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

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

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

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

22 For instance, we know from some work in

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

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

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

20 DR. ZACHAROFF: Dr. Litman?

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

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

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

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

1 outcomes.

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

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

13 DR. ZACHAROFF: Dr. Solga?

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

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

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

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

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

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

1 DR. SOLGA:

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

5 (Crosstalk.)

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

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

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

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

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

14 DR. ZACHAROFF: Dr. Terman?

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

20 DR. BONSON: Equal.

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

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

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

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

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

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

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

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

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

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

20 DR. TERMAN: Thank you.

21 DR. ZACHAROFF: Mr. O'Brien?

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

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

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

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

15 I'll let Dr. Hertz address it.

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

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

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

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

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

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

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

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

22 Just for the sake of saying this again,

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

5 (Whereupon, at 12:01 p.m., a lunch recess was
6 taken.)

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

(1:00 p.m.)

Open Public Hearing

DR. 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

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

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

12 One of our goals today for this open public
13 hearing session is for it to be conducted in a fair and
14 open way, where every participant is listened to
15 carefully and treated with dignity, courtesy, and
16 respect. Therefore, please only, when recognized by
17 me, approach the podium and speak. Thank you for your
18 cooperation.

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

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

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

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

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

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

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

22 With the addition of medications with

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

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

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

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

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

5 DR. ZACHAROFF: Thank you very much. Will
6 speaker number 2 please step up to the podium and
7 introduce yourself? Please state your name and any
8 organization you're representing for the record.

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

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

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

3 I've been doing clinical trials for almost
4 20 years. When I start a new study, I am sometimes met
5 with skepticism from the hospital staff as to whether
6 or not the study drug will help patients. After we had
7 been working with oliceridine for a couple of months,
8 we had won over the staff.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 As a patient in the hospital, I was approached

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

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

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

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

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

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

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

19 Many thanks for listening to my account.
20 Thank you.

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

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

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

9 Let me begin by saying I will celebrate
10 another year of life on the 28th and turn 35 years old.
11 At 32 years old, I was diagnosed with stage 4
12 metastatic breast cancer while still breastfeeding my
13 6-month old and third child, only son. My treatment
14 plan was very aggressive with the use of opioids as
15 part of my daily routine for multiple surgeries
16 including a double mastectomy, a liver procedure,
17 reconstructive, IV chemo, and my overall management.

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

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

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

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

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

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

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

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

22 I hope in sharing my story today that concern

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 need any assistance transferring from one bed to the
2 other.

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

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

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

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

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

9 I was discharged from the hospital on October
10 5th. My daughter happened to have an appointment that
11 day, which we had made months in advance to get a
12 tattoo as her 18th birthday present for me. She picked
13 me up from the hospital, and we went straight to the
14 tattoo shop. We were there for 4 and a half hours,
15 during which time I walked around, I sat, and I
16 conversed with my daughter.

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

1 experience with this medication.

2 The only surgery I am able to use as a
3 comparison would be from the previous year in June of
4 2015 when I had a tummy tuck for cosmetic reasons.
5 Following this surgery, I remember being in much more
6 pain with movement, and the pain medication I was given
7 kept making me fall asleep. I imagine sleep was good
8 for my recovery, but I didn't like it. I didn't like
9 that I would sleep so much and that I often felt groggy
10 and unfocused.

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

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

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

1 the record.

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

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

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

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

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

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

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

1 you're representing for the purposes of the record.

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

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

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

22 So just to begin, I just want to make clear

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

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

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

1 were GI in nature.

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

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

1 between the range of \$4000 to \$5,000 for readmission of
2 these patients.

3 That post-discharge nausea and vomiting rate
4 right now in the United States is about 38 percent. We
5 really have to do better to take care of patients to
6 avoid or minimize side effects that are associated with
7 opiates that we are currently using for pain
8 management.

9 A couple other things just to say is that I
10 think the other thing we fail to recognize is that
11 morphine has an active metabolite. And since it is
12 metabolized by 2D6 metabolic pathways, we do have a
13 variety of patients that metabolize drugs to a
14 different degree. This separation or difference in
15 metabolism often leads to an accumulation of a
16 metabolite that also has respiratory depression
17 effects. And we can't predict who those patients are
18 at this point in time. We may be able to do some
19 testing, but not enough to actually do point of care at
20 this point for every patient.

21 I think my last point would be that we need to
22 look at the opportunity to reduce medication errors

1 because often morphine will be replaced by
2 hydromorphone, and hydromorphone has the risk of having
3 a tenfold medication error discrepancy, where this
4 drug, oliceridine, has a very wide dosing range, and I
5 think will minimize that. But all in all, I think we
6 really are at a challenging point. We can do better
7 for our patients with acute pain, and this is an
8 opportunity to do so. Thank you.

9 DR. ZACHAROFF: Thank you. Will speaker
10 number 9 please step up to the podium and introduce
11 yourself? Again, please state your name and any
12 organization you are representing for the purposes of
13 the record.

14 MS. SCHWERIN: Hello. My name is savannah
15 Schwerin, and I'm a nurse and a clinical study
16 coordinator in Jackson, Mississippi. I was a neuro ICU
17 nurse for a year before becoming a study coordinator,
18 which I've been doing for a little over two years now.
19 I don't represent anyone, but Trevena has supported my
20 travel to be here today. They're not compensating me
21 for my time.

22 I would like to share with you some of my

1 experiences from my time as a study coordinator for the
2 Trevena oliceridine trial. I had different roles that
3 spanned the duration of patient participation, from
4 consenting patients in conducting screening procedures
5 to administering the investigational product and
6 monitoring for adverse events. Throughout that time, I
7 had many opportunities to gather objective data, as
8 well as listen to patient's feedback regarding their
9 perception of their hospital stay and their study
10 participation.

11 The patients enrolled in the study at my site
12 underwent various surgeries, including colon
13 resections, hernia repairs, Whipple procedures, and
14 mastectomies. Although their surgeries and
15 post-operative courses all varied, some common threads
16 were apparent among them.

17 We all know that IV opioids are great for
18 treating acute pain, and of course like many other
19 speakers have mentioned, they have many undesirable
20 side effects. The main concerns of course are nausea
21 and vomiting, constipation, itching, and respiratory
22 depression. In the next few minutes, I will highlight

1 some of the key observations I had while working on
2 this trial, including those pertaining to the side
3 effects mentioned, as well as some general points
4 regarding patient experience.

5 Several patients who had taken opioid
6 medications in the past drew comparisons between their
7 experiences with those versus oliceridine, and one of
8 the most common differences noted was that this
9 medication did not make them talk out of their head or
10 feel woozy. Many of them stated how enjoyable it was
11 to be able to visit with friends and family without
12 being drowsy or dazed while also having adequate pain
13 control.

14 For patients facing diagnoses of cancer or
15 progressive illness, which many were, or even those
16 simply recovering from a relatively uncomplicated
17 procedure, being able to spend quality time with their
18 support systems while having clarity of mind greatly
19 increased overall satisfaction with their hospital
20 stay. Other side effects observably minimal or even
21 absent in many cases were constipation, itching, nausea
22 and vomiting, and the respiratory depression.

1 In the colorectal surgery population
2 specifically, return of bowel function is an integral
3 aspect of the post-operative healing. For these
4 patients, balancing the need for pain medication with
5 the risk of impeding bowel function can be difficult.
6 For this reason, making an alternative pain medication
7 available to them which doesn't cause such a side
8 effect would be a great value and necessity.

9 Essentially, many of the patients who shared
10 feedback made note of how much they appreciated
11 oliceridine giving them pain relief without the
12 noticeable unpleasant side effects they would typically
13 expect from opioid pain medications.

14 In my experience, surgical patients are
15 usually already in an emotionally fragile state.
16 They're anxious and afraid of what is to come. The
17 overall hospital experience can truly leave a lasting
18 impression, whether good or bad. Not having the burden
19 of pain nor the burden of the side effects associated
20 with the pain medications can make an immense
21 difference in their level of satisfaction with the care
22 they receive.

1 During this trial, the impact of study
2 participation was overwhelmingly positive from my point
3 of view. As a nurse and study coordinator, keeping
4 patients safe while also meeting their healthcare needs
5 is priority number one. Working on the oliceridine
6 trial, I saw firsthand how improving pain management
7 methods can lead to better outcomes.

8 The need for effective pain relief in the
9 surgical patient population will always be present, and
10 it is of utmost importance to continue the efforts to
11 safely and adequately meet this patient need. Thank
12 you.

13 DR. ZACHAROFF: Thank you. Will speaker
14 number 10 please step up to the podium and introduce
15 yourself? And as previously stated, please state your
16 name and organization that you are representing for the
17 purposes of the record. Thank you.

18 DR. FOX-RAWLINGS: Thank you for the
19 opportunity to speak today on behalf of the National
20 Center for Health Research. I am Dr. Stephanie
21 Fox-Rawlings. Our center analyzes scientific and
22 medical data to provide objective health information to

1 patients, health professionals, and policy makers. We
2 do not accept funding from drug or medical device
3 companies, so I have no conflicts of interest.

4 New options for pain relief could benefit
5 patients, especially if they're safer than current
6 options. However, they need to be clearly demonstrated
7 to be safe and effective before approval. The data
8 provided are not completely persuasive. It is not
9 clear how well the drug works or under what conditions
10 it works. The low dose was only effective in one of
11 the two efficacy trials when analyzed by accepted pain
12 endpoints. Since replication is the key in science, we
13 can't assume that the lower dose is effective. Perhaps
14 it might be effective for some patients, but the
15 sponsor has not determined if that's true, and if so,
16 which types of patients. However, the discrepancy
17 could indicate that the results was a fluke for one of
18 the trials.

19 The drug has serious risks like all opioids,
20 and the rates of some adverse events vary between the
21 trials, which could suggest some populations or
22 surgical situations increase these risks. Given the

1 variation and effectiveness and risk for adverse events
2 between the trials, it is difficult to conclude whether
3 the benefit outweighs the risk.

4 The sponsor claims that their drug is safer
5 than morphine. It is important for you to challenge
6 that claim because the clinical trials do not yet
7 support it. Some adverse events did occur more often
8 with morphine, but the sponsor was not comparing
9 equivalent levels of pain relief. Overall, the dose
10 dependency of adverse events and pain relief mean that
11 the data do not adequately address these claims.

12 We commend the sponsor for including
13 relatively large number of black and Hispanic patients
14 in these phase 3 clinical trials. However, there are a
15 few patients that were male or over 65 years old.
16 Differences in weight, comorbidities, and other
17 characteristics could affect the efficacy and safety of
18 the drug.

19 In conclusion, there are many unanswered
20 questions about what dosages work and are safe for
21 which patients under which conditions. We know that
22 there is an epidemic for opioid use, so these questions

1 must be answered before a decision is made about
2 whether or not to approve this opioid. Thank you.

3 DR. ZACHAROFF: Thank you. Will speaker
4 number 11 please step up to the podium? Introduce
5 yourself, state your name, and any organization you are
6 representing for the record.

7 DR. LeVON: Good afternoon. My name is Hohn
8 LeVon. I'm a clinical pharmacist of 20 some years,
9 many of which were in a hospital. I have not been
10 compensated. Trevena has not paid for my time or air
11 travel. But if people would like to, feel free. I'm
12 more than happy for that assistance.

13 First and foremost, thank you for your time
14 and what you do to protect the public and to advance
15 the art and science of medicine. After listening to
16 all the information and differences and definitions and
17 approaches on how you measure efficacy and the benefits
18 of using sufficiency versus magnitude alone, as well as
19 different approaches to mathematical analysis, what I
20 would like you to consider now is who you are serving
21 and helping and who you who will benefit from this drug
22 being available.

1 One population not discussed today, and one
2 that is very common and very important to consider for
3 this medication, are those that suffer from allergies,
4 specifically morphine and hydromorphone allergies. We
5 will all agree that drug-related allergy events are
6 significant and very common occurrences that
7 unfortunately thousands of people die from each and
8 every year. And to that point, I want you to reflect
9 and consider this everyday hospital occurrence, that a
10 patient has a morphine allergy and needs an
11 alternative.

12 Today, you are only left with hydromorphone
13 and fentanyl. As a pharmacist, I would cringe when I
14 would call the nurse or the physician to alert them of
15 a morphine allergy, and I would just hear them say,
16 "Just give hydromorphone," because fentanyl was not
17 approved for use on that floor or because fentanyl
18 required respiratory support.

19 Remember, hydromorphone is chemically very
20 similar, and many patients are cross-sensitive, so
21 obviously there's that concern. By approving
22 olliceridine, you would give the practitioners and

1 patients a chemically unique alternative, but without
2 the morphine allergy risk.

3 In closing, I want to add that we spent a lot
4 of time today discussing whether oliceridine is better
5 than morphine and whether there is statistical
6 significance to be better than morphine. But when
7 you're allergic to morphine and hydromorphone, morphine
8 is not an option. And being statistically significant
9 better than morphine in efficacy doesn't matter. What
10 matters, as I believe they have shown with their
11 1800-plus patients, is that it is safe, it is effective,
12 and would be a welcomed new option for a large
13 population of patients that currently don't have an
14 equivalent alternative.

15 I thank you for your time, and I encourage you
16 to approve oliceridine and take part in advancing
17 medicine and increasing options.

18 **Clarifying Questions (continued)**

19 DR. ZACHAROFF: Thank you.

20 The open public hearing portion of this
21 meeting has now concluded and we will no longer take
22 comments from the audience. The committee will shortly

1 turn its attention to address the task at hand, the
2 careful consideration of the data before the committee
3 as well as the public commentary we just heard.

4 We do have just a few brief minutes. If
5 anybody had any clarifying questions for the FDA please
6 let us know. We'll give you the opportunity. We're
7 going to keep this very brief so we can move on with
8 the charge to the committee.

9 Dr. Kaye?

10 DR. KAYE: Thank you. Dr. Kilgore, I had a
11 question. If you took out the highest dose of this
12 drug, would the conclusions that you presented to us in
13 terms of respiratory effects be the same or different?

14 DR. MAYNARD: This is Janet Maynard from the
15 FDA. When we analyzed the safety and efficacy, clearly
16 we looked at the 3 doses of oliceridine that the
17 applicant randomized patients to in their trials
18 because we thought it was very important to look to see
19 if there was a dose response for safety and efficacy.
20 And we find that that information is helpful as you
21 think about overall benefit-risk considerations.

22 Your question about whether or not if we

1 remove the 0.5, if that would change our conclusions.
2 I don't think so. We know what the results are for the
3 0.5-milligram dose in terms of efficacy and safety.
4 And as Dr. Kilgore alluded to in her presentation,
5 there were multiple changes to the applicant's proposed
6 dosing during the review cycle, including when the
7 application was initially submitted, they were seeking
8 approval for the 0.5-milligram dosing regimen. So this
9 is a change that happened during the review cycle.

10 DR. ZACHAROFF: Thank you. Dr. Alexander?

11 DR. ALEXANDER: And maybe this will come out
12 during the discussion. But it would help me if the FDA
13 could help me at least in my thinking to understand
14 what's necessary for approval. Is this a question of
15 whether oliceridine is safe and effective period, like
16 better than placebo, or better than morphine? Is it a
17 noninferiority question or a superiority question if
18 we're comparing it to an active comparator like
19 morphine?

20 DR. HERTZ: That's a pretty good question.
21 The standard for approval is evidence of efficacy. And
22 for the most part, analgesics are compared to placebo,

1 and we don't disagree that there's evidence of
2 efficacy. Then we have to look at safety, and the
3 benefits have to outweigh the risks. So if you look at
4 the risk and benefit of the drug, that's the
5 requirement for approval.

6 In this case, the objective of developing this
7 novel type of agonist was to demonstrate the ability to
8 differentiate safety and efficacy, and that's why we're
9 looking at it relative to morphine. If we were going
10 to ignore the data for the 0.5 dose, what we would have
11 is evidence of efficacy for the 0.1 in one of the
12 studies, 0.35 in both of the studies, and a safety
13 profile that looks the way it does. But the question
14 then is, if we had lowered the dose of morphine, would
15 we have had the same profile?

16 That doesn't really answer your question, does
17 it? The fundamental requirement for approving a new
18 drug is evidence that there's a favorable risk-benefit
19 for the product when used in the intended population
20 according to labeled instructions.

21 DR. ALEXANDER: Can I just make one other
22 question? There was a statement -- I think it was one

1 of Trevena's presentations -- that the labeling is not
2 going to make statements comparative to morphine.

3 DR. HERTZ: That doesn't mean the company
4 won't. It just means we won't put it in the label.

5 DR. ZACHAROFF: Just two more, and then we'll
6 move to the charge to the committee. Dr. Goudra?

7 DR. GOUDRA: Hi. Dr. Goudra from U Penn. One
8 or two questions. Unlike morphine, oliceridine is
9 metabolized through the cytochrome P450. And I see
10 about 10 percent of the patients in the information
11 given by Trevena are kind of low metabolizers. Did the
12 FDA analyze the data between normal metabolizers versus
13 low metabolizers in terms of adverse events?

14 DR. HERTZ: I don't think we received any data
15 looking at different phenotypes for the CYP enzymes,
16 but perhaps we did.

17 DR. VIOLIN: I'd be happy to provide extra
18 data if that would be useful to you.

19 DR. GOUDRA: [Inaudible - off mic].

20 DR. VIOLIN: Oh, the extensive metabolizers.
21 We did evaluate the pharmacokinetics as well as the
22 safety of oliceridine in extensive versus poor 2D6

1 metabolizers. And while the clearance is slowed in 2D6
2 poor metabolizers, because the drug is given as needed,
3 what happens is they dose less frequently. So the
4 maximum concentration of Cmax did not change in the
5 phase 3 studies, independent of 2D6 status.

6 I'd like to clarify one other point as well,
7 which is we tried to be clear that when we were
8 developing oliceridine, the primary endpoint, the
9 prespecified primary endpoint that did succeed in both
10 studies for both point 0.1 and 0.25 was something that
11 we believed the agency was not opposed to.

12 They told us at the end of phase 2 meeting
13 they did not object to it, provided there was
14 additional evidence to support the findings, which we
15 think we have and have shared. And that that
16 demonstration of efficacy would be sufficient to show
17 the drug works. And the overall safety profile that is
18 characterized as a holistic assessment would be put in
19 context of efficacy demonstrated versus placebo.

20 All the comparisons to morphine were a
21 scientific question and an important scientific
22 question. But we did not design the studies to support

1 approval in that way. That's why the endpoints were
2 structured the way they were. That's why the studies
3 were powered the way they were. And that's why we've
4 tried to keep those questions separately.

5 The data we think that supports approval is
6 very robust and statistically significant, and we agree
7 that some of the improvements, while very encouraging,
8 do not meet regulatory thresholds. And that's why we
9 say we don't believe that they merit comparative claims
10 in labeling, but that's separate from the approval
11 question.

12 DR. ZACHAROFF: Thank you.

13 DR. GOUDRA: Just one more question.

14 DR. HERTZ: Excuse me. I just want to
15 clarify. My understanding is that the comparisons with
16 morphine were part of the prespecified statistical
17 analysis plan. And presumably had they been
18 successful, you would have sought to have them in
19 labeling?

20 DR. VIOLIN: Our understanding of the key
21 secondary endpoint, which was the respiratory safety
22 burden, because it was not validated, that was not

1 going to be acceptable for safety comparison.
2 Nonetheless, we thought it was important to test. We
3 thought we generated a lot of interesting data, and
4 it's something that we would welcome further
5 discussions with the agency in terms of postmarketing
6 studies.

7 DR. GOUDRA: You're not asking for approval in
8 pregnant patients do you? I don't see any data on --

9 DR. VIOLIN: No, we've not studied that.

10 DR. GOUDRA: Okay. Thanks.

11 DR. ZACHAROFF: Just two more. Ms. Phillips?

12 MS. SHAW PHILLIPS: Thank you. In the
13 agency's discussion, I think there was a comment
14 related to the phase 2, indicating that in addition to
15 the prespecified rescue medication, there were other
16 medications that might have made assessment of
17 acceptability of the pain control, difficult to assess.

18 Could you provide additional information on
19 that?

20 DR. MAYNARD: Janet Maynard from FDA. Do you
21 mean in the backgrounder there was --

22 MS. SHAW PHILLIPS: There was a comment this

1 morning about --

2 DR. MAYNARD: But I think that was in
3 reference to the phase 3 studies.

4 MS. SHAW PHILLIPS: Okay. Could you comment
5 on those? I think clarifying that endpoint of not
6 needing any rescue medication and all that is really
7 important.

8 DR. TRAVIS: Yes. The sponsor's original
9 analysis ignored use of -- James Travis, statistical
10 reviewer. The sponsor's original analysis ignored the
11 use of non-protocol specified, and there were quite a
12 few people who used it.

13 I have a backup slide. Is it numbered from
14 the -- I think slide 36; 37 then. There we go.

15 This is the rescue medication that was used in
16 the phase 3 program, so anything that wasn't etodolac
17 was not taken into account for their responder
18 definition. The analyses I presented included them as
19 non-responders because we don't see the point of
20 discriminating between etodolac and anything else.

21 MR. PETULLO: This is David Petullo --

22 DR. VIOLIN: If I might just respond very

1 quickly, I just wanted to remind the committee that the
2 data we presented in our core for the primary endpoint
3 did include non-protocol specified --

4 MR. PETULLO: I just want to put out that this
5 didn't change our overall conclusion. It might have
6 changed the numbers slightly, but it wasn't a major
7 issue.

8 DR. VIOLIN: When the agency brought this up
9 in review, we agreed. We included in the analysis that
10 conclusions did not change.

11 DR. ZACHAROFF: Thank you. All right, lastly,
12 Dr. Fischer?

13 DR. FISCHER: Thanks. I'll be quick. I'm
14 Mike Fischer, Brigham Women's in Boston. In terms of
15 the respiratory side effects, we already discussed the
16 differences in how those were defined, and that's been
17 covered. Thinking about the kinds of patients likely
18 to be receiving this in general practice, were there
19 any analyses of the respiratory safety events profile
20 focusing on patients with any kind of preexisting risk?

21 I know there were some patients with sleep
22 apnea. I don't know if patients with preexisting

1 pulmonary disease were completely excluded. I don't
2 know if you have anything on that.

3 DR. MAYNARD: As Dr. Kilgore mentioned, we
4 focused on the respiratory safety in the phase 3
5 trials. And generally, as the sponsor has mentioned,
6 the populations in phase 3 trials tend to be slightly
7 on the healthier side usually because they frequently
8 don't have as many comorbidities as some other patients
9 in practice.

10 The sponsor did provide data from study 3003,
11 which has information about respiratory safety and what
12 they thought would be a more real-world setting. The
13 problem with that study is there's no comparator, so
14 it's very difficult for us to make any definitive
15 conclusions on what the respiratory safety would look
16 like in that sort of setting because we really don't
17 have comparative data to assess that.

18 DR. ZACHAROFF: Okay. Thank you.

19 We will now move to Dr. Sharon Hertz, who's
20 going to provide us with a charge to the committee.

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

22 DR. HERTZ: So you've heard a lot today about

1 this new product. You've heard about the applicant's
2 data and interpretation of the safety and efficacy for
3 this novel G-protein ligand biased agonist of the new
4 opioid receptor. And you've heard our interpretation
5 of the data and where those differ.

6 We acknowledge that the nonclinical and
7 experimental data were supportive that there could be a
8 differential effect on some of the adverse events and
9 the clinical efficacy, but where we disagree is how
10 well, if at all, those were described in the clinical
11 studies. And we also have some disagreement with
12 respect to understanding the relative efficacy and
13 safety of the active comparator. But it was brought up
14 that the standard for approval is not that a new drug
15 has to be the same or better than an existing drug. It
16 should be approvable on its own merit based on the
17 overall data and the risk and benefit balance for that
18 product.

19 So as we go through the questions -- there are
20 fairly standard questions now that many of you can
21 probably recite -- in terms of what you think about the
22 efficacy, the safety, what you think about the public

1 health risk, scope, and novel opioid, and what you
2 think about the overall balance and whether or not it
3 supports approval, please consider that in the context
4 of your experience and how you understand the product
5 will be used based on what's been described today.

6 As always, while the vote is very interesting,
7 what's even more interesting is to hear the thoughts
8 that you have in response to these questions and the
9 thoughts that you have that support how you ultimately
10 vote. Thank you very much for being here today.

11 **Questions to the Committee and Discussion**

12 DR. ZACHAROFF: Thank you. So as we start to
13 address the questions, I would like to encourage all of
14 the panel members to participate. I'd like to
15 encourage you to give your thoughts and perspectives
16 with respect to the question without saying how you're
17 going to vote; really, just to give your impressions
18 about the question at hand and what your thoughts are,
19 and to use your expertise, to the degree that you can,
20 to apply the discussion questions to your specific
21 areas of expertise, and give your perspectives about
22 what you really think given your area of expertise.

1 So with that, we will move on to the first
2 question. Discuss the efficacy of oliceridine and
3 whether the data provides substantial evidence for
4 efficacy of oliceridine for the proposed indication of
5 the management of moderate to severe acute pain in
6 adults for whom an intravenous opioid is warranted.

7 Panel members, discussion?

8 DR. ZELTZER: Are you going to go around the
9 room?

10 DR. ZACHAROFF: We could go around the room.
11 You can turn your cards. What would you like?

12 Dr. Solga?

13 (Laughter.)

14 DR. SOLGA: Honestly, I wasn't prepared to
15 make a statement, but there's some evidence for
16 efficacy. There's no doubt about it. There's the
17 step-wise dose response. There's no doubt it's an
18 effective medicine versus placebo. I'm still
19 struggling with the context and whether or not that's
20 acceptable in the overall scheme of regulatory
21 approval.

22 DR. ZACHAROFF: Thank you. Dr. Zeltzer?

1 DR. ZELTZER: It seems as though there are two
2 issues in terms of efficacy. I think that the product
3 has been shown, at least in terms of comparison to
4 placebo, efficacy in the situation for acute moderate
5 to severe pain, but in a relatively healthy population.
6 Given the procedures that were studied, those
7 procedures are generally performed not in the kind of
8 population that one of the audience had talked about,
9 the surgeon who's seeing obese patients who have heart
10 disease, the multi- complicated, complex patient.

11 I guess in the relatively healthy patient for
12 a relatively non-major surgical procedure, I think
13 efficacy has been shown, at least to my satisfaction.
14 Now, the request is for up to 40 milligrams, and I
15 think one of the slides that you showed, if you look at
16 the maximum, or maybe it was FDA's, it was
17 24 milligrams even though the request is for
18 40-milligram maximum in that time period.

19 So I don't know if that creates a problem, but
20 if the indication in terms of efficacy is for all kinds
21 of surgeries or all kinds of situations,
22 short-term moderate to severe pain, I guess I would

1 feel more comfortable if there were a study in a more
2 complex population because that's the population, if
3 you look more broadly, that this drug will end up being
4 used.

5 So it's a question. And I'm sitting here like
6 this because I think you did show efficacy for the
7 populations studied.

8 DR. ZACHAROFF: Thank you. Dr. Litman?
9 Again, we're limiting this just to the discussion
10 around the efficacy.

11 DR. LITMAN: Thank you. Ron Litman. I do
12 agree. I think that the phase 3 study showed efficacy,
13 but I have a couple of thoughts about that. The first
14 is that this is not real life. Real life is just like
15 we talked about before where you titrate. And in the
16 clinical setting, when we're treating a patient with
17 pain, it's never just one dose. It's many doses. It's
18 consideration of lots of different factors.

19 Unfortunately, there's just no way to find the
20 truth behind what will happen with this drug once it's
21 being used. It takes many different patients over
22 years. So clinicians will ultimately decide for

1 themselves.

2 The second thing is this is really just based
3 on one phase 3 study and a couple of open labels. I
4 was a little concerned during the public comments when
5 several of the commentators talked about both nurses
6 and patients the way they were approached. And I would
7 hope that this was the open label, not the blinded
8 study, how here's this miracle drug that's going to
9 give you less nausea and make you feel so much better
10 than the real drugs we use. I mean, if that was truly
11 in the phase 3 study, that's the exact opposite way to
12 do a clinical study, of course.

13 The third aspect I wanted to comment on is the
14 marketing, and that's one of the things that I was
15 thinking about before -- and Sharon alluded to it
16 before with her comments about what the company could
17 say about the drug. As the law stands now, a drug
18 company can market a drug based on truthful
19 information, depending upon of course the district
20 you're in and whether or not it's on the label. But
21 even in the districts where it was found by the Caronia
22 case to be free speech, it's only free speech if it's

1 truthful.

2 So if the truth is that it's not better than
3 morphine, then they shouldn't be able to market it as
4 such. Now, we all know in the real world that doesn't
5 always occur. History has shown that does occur in
6 many different products. So those are my comments, and
7 I'll let other people contribute.

8 DR. ZACHAROFF: Thank you. Dr. McCann?

9 DR. McCANN: Dr. McCann, and I'm speaking up
10 because you asked everybody to speak up. I think the
11 drug is efficacious certainly against placebo. There's
12 been no evidence at all to suggest that it's not.

13 DR. ZACHAROFF: Thank you. Dr. Terman?

14 DR. TERMAN: Thank you. And I also think that
15 it shows efficacy, certainly the 2a fixed dose shows
16 that you can get more pain relief if you push the dose.
17 However, if you asked me if there's any advantage over
18 morphine, I'd say I don't have any idea because I think
19 all of the PCA studies more clearly by chance are
20 designed easier for patients to titrate to their
21 sufficient level of analgesia. If you set the dose
22 such that they only hit it once an hour, you're going

1 to have an awful hard time titrating because they're
2 going to have to decide, well, am I willing to risk the
3 side effect?

4 The other thing that I like about the efficacy
5 is the rapid onset. It really does appear to be
6 working very quickly, 5 minutes in some other data.
7 That should be useful for a patient who's got a 6-
8 minute lockout on their PCA.

9 DR. ZACHAROFF: Thank you. Dr. Shoben?

10 DR. SHOBNEN: I have a couple of comments about
11 efficacy. The first is to say I actually really liked
12 the responder. In point, we talked about it at a
13 previous advisory committee, this problem of imputing
14 the scores for patients with rescue medications. And
15 this sort of responder endpoint both addresses that
16 concern and gets at the idea that the sponsor talked
17 about, about treating pain disorder sufficiency and not
18 trying to get to a goal of no pain, which I think most
19 people at least would agree that's important.

20 So if you agree with the responder, then I
21 think they have met efficacy for both 0.1 and 0.35
22 dose. That said, it's clear to me that there are

1 questions around 0.1 dose and whether or not that
2 efficacy compared to placebo would be enough to -- that
3 that benefit would be enough to outweigh any potential
4 risk of 0.11 I think the efficacy for 0.35 is
5 certainly stronger, particularly using the actual
6 numerical scores with different imputation as
7 demonstrated by the FDA reviewer

8 Yes, so I think those are my comments.

9 Thanks.

10 DR. ZACHAROFF: Thank you. Dr. Goudra?

11 DR. GOUDRA: Dr. Goudra from Penn medicine. A
12 couple of things. People are talking about efficacy
13 compared to placebo. In real life, we don't give
14 placebo. We use morphine or dilaudid or whatever it
15 is. From that point, it looks like if the question is
16 substantial evidence for efficacy and the dose that
17 Trevena is seeking approval for, I don't think there is
18 substantial evidence to show that it is as effective as
19 morphine. Like it or not, that's what we should be
20 looking at in terms of efficacy, not the placebo.

21 Maybe if the dose is increased to improve the
22 efficacy, it probably loses the selectivity in terms of

1 G-protein protein versus beta arrestin, and maybe
2 they'll address [indiscernible] go up. That's my
3 feeling.

4 DR. ZACHAROFF: Thank you. Dr. Alexander?

5 DR. ALEXANDER: Thank you. John Alexander
6 from duke. I too think there's clear evidence of
7 efficacy versus placebo. There's further evidence from
8 the dose response within the oliceridine doses. It's
9 less clear to me whether there's an efficacy benefit,
10 or equivalency, or noninferiority of oliceridine
11 compared to morphine.

12 I've just been thinking, the whole premise of
13 the development program that we heard is that
14 oliceridine is going to be just as effective as
15 currently available narcotics -- they studied it
16 against morphine -- but with improved safety, which
17 we're going to come back and talk about further.

18 I've been thinking through that the key
19 question about whether there's roughly equivalent or
20 noninferior efficacy compared to morphine, it seems to
21 be dependent on which method of efficacy analysis is
22 chosen, the one the sponsor did or the one that the FDA

1 did. And I've been thinking about and haven't figured
2 out yet which one is more clinically relevant. Which
3 one's more relevant to how we dose narcotics or how
4 people who do dose narcotics like this -- I
5 don't -- dose narcotics clinically, using a threshold
6 or a magnitude of effect?

7 DR. ZACHAROFF: Thank you. Dr. Fischer?

8 DR. FISCHER: Mike Fischer, Boston. Coming
9 back to the question of substantial evidence of
10 efficacy, I'd echo Dr. Shoben's point that the
11 substantial evidence threshold seems harder to justify
12 for the 0.1 dose. And because the other component of
13 the application is the 0.35 dose, the thing I'm
14 grappling with is do we have substantial evidence when
15 we think about the range of patients who will be
16 getting this in usual practice? Again, thinking about
17 some of the public comments, the patients who've been
18 on chronic opioids, the patients who are obese and
19 getting surgery, and some of the others, do we have
20 substantial evidence of efficacy for those kinds of
21 patients because later we'll be of course weighing that
22 against the safety. So those are a couple of the

1 points I'm chewing over.

2 DR. ZACHAROFF: Thank you. Dr. Kaye?

3 DR. KAYE: Alan Kaye from LSU, New Orleans. I
4 think it's clear that there's evidence for efficacy
5 versus placebo. I just would say that 15 years ago, we
6 moved away from morphine to use other agents in this
7 setting because we didn't think morphine was so great.
8 So not to confuse everyone, but it really wouldn't be
9 something that we would measure in our practice against
10 morphine. We would probably look at things like
11 dilaudid and some of the other agents that have better
12 profiles.

13 DR. ZACHAROFF: Thank you. Dr. Warholak?

14 DR. WARHOLAK: I agree with some of my
15 colleagues that the 0.1 dose, the efficacy is harder to
16 show. In the FDA briefing packet on page 12, it
17 indicated that the 0.1 dose was not statistically
18 significant but statistically significantly better than
19 placebo. Now we're not asking for approval for the
20 0.5, so that only leaves the 0.35. So I'm not sure
21 exactly where that leaves us.

22 DR. ZACHAROFF: Thank you. Dr. Solga?

1 DR. SOLGA: I'm sorry. I wasn't quite ready
2 to speak earlier when you called. Just to follow on to
3 an unprepared statement maybe as a flip statement, many
4 others have pointed out that maybe placebo just isn't
5 the right comparator, even though that's the statutory
6 expectation. As Dr. Goudra points out, nobody
7 prescribes placebo.

8 Earth has many pharmacologic and
9 non-pharmacologic opportunities for pain management.
10 Not to sound flip, but one of my liver colleagues who
11 had a foot surgery and was suffering in pain, couldn't
12 sleep at night, and his Percocet ran out. I said,
13 "What did you do?" And he said, "Drink scotch, and
14 then I drank more." So that also has a dose-response
15 curve that folks recognize and use.

16 So the reality of 0.1, 0.35, and 0.05 differed
17 on dose-response curve efficacy to placebo is
18 important, but almost, gee whiz, so what, compared to
19 the big picture of benefit-risk considerations.

20 DR. ZACHAROFF: Thank you. Ms. Phillips?

21 MS. SHAW PHILLIPS: I think a lot of my
22 comments have already been made, but I think the PK

1 shows that this is a drug that can have a very fast
2 effect. So it has an effect, and I think there's a
3 benefit there on the whole range of sufficiency. If
4 patients can get that effect and be able to manage
5 their pain in a way that is patient-centric, where they
6 have control over that decision point, and ultimately
7 use less of an opioid medication, that's a good thing.

8 So I think in today's era of multimodal pain
9 management and trying to minimize the bad effects of
10 any medications that we're on, if the patient has more
11 control over that and gets a suitable level of efficacy
12 in a way that minimizes the side effects, even if
13 that's due to a lower dose, I think there is an
14 efficacy benefit there.

15 DR. ZACHAROFF: Okay. And my comments mirror
16 pretty much what I've heard all of you say, so I don't
17 really have anything to add. But just to summarize to
18 make sure I got this right -- I'm sorry.

19 Mr. O'Brien, I didn't see you there.

20 MR. O'BRIEN: I don't have much to add to it,
21 except I would say from my patient perspective, I
22 agree. Substantially. I struggled with the word

1 "substantial" that's there for the evidence. However,
2 I would say from a patient, give me 0.35. I don't want
3 0.1. Don't bother with that. It's wasting my time.
4 And I'm very fearful of getting 0.5. There's a threat
5 there that I see.

6 DR. ZACHAROFF: Thank you.

7 Just to summarize the comments to make sure we
8 captured them adequately, if I leave anything out,
9 please let me know. By and large, people are satisfied
10 that from an efficacy perspective, oliceridine
11 demonstrated efficacy in healthy individuals but not
12 necessarily complex patients with multiple medical
13 problems. And while it was better than placebo, that's
14 probably not surprising because anything would likely
15 be better than placebo. And in managing pain, there
16 really is no situation where you use a placebo to
17 manage someone's pain.

18 From a real-life perspective, the likelihood
19 is that this drug will be titrated. So it may be
20 difficult initially to wrap our heads around how much
21 of this medication is actually used, especially when
22 we're not necessarily recording how many times the

1 patient presses the button. And if they can press it
2 every 6 minutes and get a dose every 6 minutes, it may
3 take a while.

4 So real life is going to be a titration kind
5 of situation and how much medication is actually needed
6 to treat different people's pains for different reasons
7 may be very different.

8 People mentioned the fact that the relief is
9 dose related. I think the general consensus of the
10 panel was that there weren't really many impressions
11 about superiority to morphine in this case. There was
12 superiority to placebo.

13 The rapid onset definitely is a quality of
14 this medication that poises it to be a value in
15 patients who have an intravenous access, who do have
16 acute pain of this severity. There still remains the
17 question about the 0.1-milligram dose and its ultimate
18 efficacy, that the data presented wasn't really
19 substantial to make people overwhelmingly feel that the
20 0.1 milligram was going to save the day by itself and
21 it might end up being the point 0.35. As we heard
22 Mr. O'Brien say, he said, "Give me the 0.35," and let's

1 get down to brass tacks.

2 I guess lastly, the overarching question is,
3 is evidence for use in real-life patients that we're
4 likely to see enough to give us confidence with respect
5 to the efficacy?

6 That's my summary of the discussion for
7 question 1. Did I leave anything out?

8 (No response.)

9 DR. ZACHAROFF: Okay. So we're going to move
10 on to discussion 2. And good job, by the way, of not
11 saying anything about voting. We want to keep it just
12 to the discussion, so kudos for that.

13 Question 2, discuss the safety profile of
14 oliceridine and whether the safety profile of
15 oliceridine is adequate to support approval of
16 oliceridine for the proposed indication of the
17 management of moderate to severe acute pain in adults
18 for whom an intravenous opioid is warranted.

19 We really want you to think specifically about
20 these four categories from a safety perspective:
21 general safety, hepatic safety, respiratory safety, and
22 QT prolongation perspective.

1 To save me from calling on anybody, anybody
2 have anything to say? Dr. Litman?

3 DR. LITMAN: Thank you. Ron Littman. Just
4 going down the list here real fast, the database of I
5 forget how many -- a couple thousand patients, there's
6 just no way to know, honestly, what the right number
7 is. It seems, my general gestalt from looking at the
8 data and looking at the number of patients, that it is
9 relatively safe. And relatively is a really hard term
10 to define here because we're thinking about it compared
11 to placebo, but we're also thinking about it compared
12 to other opioids.

13 Hepatic safety is a little bit alarming
14 because of a couple of signals in the data, and I don't
15 have the expertise to be able to reasonably comment on
16 that for sure. But I would be very interested in
17 further phase 4 studies looking at what happens down
18 the line when more patients take it, and do these few
19 patients that popped out before that we discussed, is
20 that really a signal? Is that really different from
21 other drugs?

22 Respiratory, again, we talked about the

1 hypercapnic test, and that's just such an artificial
2 test. It really is just so preclinical in a sense even
3 though it's on humans. Honestly, Dr. Webster, I'm
4 sorry. I'm not convinced that the way that it was
5 conducted was really rigorous or accurate. It may have
6 been. I just couldn't tell from this data.

7 But on the other hand, just looking at all the
8 data cumulatively, I don't have any considerations,
9 except if further studies or further experience showed
10 that these doses, which we think may have been less
11 efficacious than morphine, in real life that we have to
12 use higher doses in order to control our patient's
13 pain. And that we don't know. And I don't have any
14 concerns about QT prolongation.

15 DR. ZACHAROFF: Thank you. Dr. Higgins?

16 DR. HIGGINS: I could not help but be
17 persuaded by the FDA analyses. I find them highly
18 persuasive. And I can't also disentangle the
19 comparison to morphine as I think about all the data
20 cumulatively. With respect to hepatic safety, I find
21 the same frequency of problems between oliceridine and
22 morphine and the treatment groups. With respiratory

1 safety, no statistically significant difference between
2 morphine, and again, insufficient data I think to
3 really evaluate this.

4 Under QT prolongation, I would have liked to
5 have seen more ECG data, and I think that was
6 inadequate. And I just think overall there was not
7 enough data to really evaluate that as well. Those are
8 my statements on the four areas.

9 DR. ZACHAROFF: Thank you. Dr. Goudra?

10 DR. GOUDRA: Dr. Goudra from Penn medicine. A
11 couple of issues here. One, as anesthesiologists, we
12 do end up loading up these patients interoperatively to
13 prepare them for post-op pain. So as a result, we do
14 not necessarily titrate them in the 0.1 or 0.25,
15 whatever. I don't know whether Trevena wants us to do
16 that interoperatively like we do [indiscernible]
17 morphine.

18 If we do that, unlike morphine, there is a
19 problem of 10 percent of the population who only half
20 metabolizes. As a result, their effective
21 concentration is almost twice. So would they be
22 subjected to more problems as far as safety's

1 concerned, whether it is respiration or -- so that's
2 one aspect.

3 Second, yes, in clinically recommended doses,
4 hepatic safety and QT prolongation may not be an issue.
5 But considering it is an opioid and it will be
6 subjected to the same abuse problems like other drugs,
7 if somebody either accidentally or deliberately injects
8 it, will we have the same QT prolongation related
9 problems where we add cardiac and hepatic toxicity over
10 the respiratory depression already? Thank you.

11 DR. ZACHAROFF: Thank you. Dr. Terman?

12 DR. TERMAN: Sure. Thank you. Let me say
13 that I am a big fan of the agonist biased story, and I
14 followed it in my basic science lab, participating a
15 little bit since Dr. Bond's first beta arrestin
16 knockout paper in Science showed a potentiation of
17 morphine, and actually along with that suggested a
18 decrease in tolerance.

19 I'm very interested in this class of drugs,
20 and I'm pleased to see that the work continues. In
21 terms of other, this is the first. There's a BCM [ph]
22 compound and a whole list of compounds from

1 Scripps [ph] that have -- and I'll talk about what I
2 know best -- some association with respiratory
3 depression; that is the decreased arrestin activation
4 seems to be correlated with a safer experience, at
5 least for rats, mice, and monkeys. And it hasn't
6 gotten to humans quite yet.

7 However, having said that, although I did like
8 the new slide that showed the better analgesia than
9 morphine early on, despite a similar respiratory
10 depression as morphine, whether or not cold pressor is
11 a clinically relevant test, I've used it as such, and
12 so I have a hard time pretending that it's not. But I
13 don't think that there's anything in the more recent
14 clinical studies, as I said before, because of relative
15 more morphine being given. I don't think we can say
16 anything about the respiratory safety.

17 What I was pleased about and what I asked
18 about was whether this rapid onset drug that does cause
19 euphoria might have any more abuse potential than
20 morphine, a slower onset drug. And everyone seemed to
21 agree that that was not the case. So that's a good
22 thing for me.

1 In terms of the hepatic safety and QT
2 prolongation, I don't know. I have to just trust the
3 experts. So that's the end of my comments. Thanks.

4 DR. ZACHAROFF: Thank you. Dr. McCann.

5 DR. McCANN: I think all the data that's been
6 presented demonstrates that it appears to be pretty
7 safe, but my concern is that they haven't met the
8 threshold. So I asked that earlier question about 350
9 people and whether that was just a number pulled from
10 thin air or actually had some statistical basis, and I
11 guess it's got a very soft statistical basis. But they
12 haven't enrolled 350 people at the 40-milligram per 24
13 hours dose, which is what they're asking permission
14 for.

15 It gets back to When I look at the other
16 safety aspects, the safety database seems fine. The
17 hepatic, I can't really ascertain but it appears safe.
18 Respiratory, I'm not worried about. But the QT
19 prolongation, I think in the real world, people are
20 going to titrate this to effect because that's what we
21 do for other narcotics. So it would be relatively few
22 patients that would get more than 3 milligrams, but

1 there might be some that had prior exposure to
2 narcotics that would get the 6 milligrams. We don't
3 really know enough about that in terms of QT
4 prolongation.

5 So I think it would be -- since Dr. Hammer and
6 others have mentioned that this is not a perfect drug,
7 it may be an improvement. I don't know that it's
8 necessary to cut corners before we get the adequate
9 data. And again, to go to Dr. Zeltzer's point, we
10 don't know anything about how this drug behaves in
11 elderly great-grandmothers. Thank you.

12 DR. ZACHAROFF: Thank you. Dr. Fischer?

13 DR. VIOLIN: Can I make one comment? I just
14 wanted to
15 reiterate that in ATHENA, we did enroll hundreds of
16 patients over the age of 65. We enrolled patients with
17 sleep apnea. We had a very high enrichment. We really
18 care about this problem, so we have those
19 subpopulations and didn't see any difference in the
20 safety profile. I just wanted to remind you of that
21 data. Thank you.

22 DR. McCANN: Okay.

1 DR. ZACHAROFF: Dr. Fischer?

2 DR. FISCHER: Great. Thanks. Mike Fischer
3 from Boston. The question I think to me is the
4 adequacy of the data, especially, picking up on some of
5 what Dr. McCann was just talking about, the overall
6 flavor of the presentations, the public comments as
7 well is really focused on the idea that this is going
8 to be a medication. I realize that there will be
9 what's said on the label, but that this is likely to be
10 used for those patients who are difficult to treat. I
11 mean, that's the flavor we've been getting all day,
12 that we need something for those difficult to treat
13 patients. And those are patients who, for a variety of
14 reasons, are either likely to have more complicating
15 factors even then in the open-label study or end
16 up -- because we're going to be titrating in clinical
17 practice, with much higher doses.

18 So in thinking about some of the signals we
19 have that can't quite be spoken to authoritatively,
20 especially those looking at the FDA presentation where
21 there is a better respiratory safety signal because
22 we're not using as potent an analgesic dose of

1 oliceridine in the trial compared to morphine, I worry
2 that the safety database we have at present does not
3 represent the dose range and population that will be
4 getting this once the drug's been in clinical practice
5 for a while.

6 We can't do everything. That's what phase 4
7 studies are for, but it does make really salient the
8 question Dr. McCann was raising, do we have enough
9 information on the patients who are going to end up
10 getting titrated to pretty substantial exposures of
11 this drug out in real-world practice.

12 DR. ZACHAROFF: Thank you. Dr. Zeltzer?

13 DR. ZELTZER: There was one point that maybe I
14 missed. In your presentation, at least by this slide,
15 or again maybe -- you want approval for up to 40
16 milligrams. And I thought the actual data presented,
17 the maximum was actually 24 milligrams. So in terms if
18 we're thinking safety -- can somebody -- can you speak
19 to that?

20 DR. VIOLIN: I'm happy to if that's okay. so
21 the FDA was very clear. They wanted to see 350
22 patients with the highest and longest exposure to

1 determine what the maximum daily dose should be. We
2 had proposed -- as you've heard, we've been in
3 discussion with the agency. Most recently, we propose
4 40 milligrams as the median of exposure in that group.
5 The FDA has pointed out the 27 milligrams is the
6 minimum. So that's the number at which there are 350
7 patients, have had at least 27 milligrams in the first
8 day.

9 Now, in the ATHENA population, that's where
10 multimodal analgesia was used, so that most closely
11 reflects how you might use this in your practice. 27
12 milligrams was -- sorry. About 80 percent of patients
13 used 27 milligrams or less.

14 So we're proposing 40. We consider this a
15 dialogue with the FDA. Anywhere in that range is going
16 to satisfy the great majority of patients in the
17 multimodal context.

18 DR. ZACHAROFF: Thank you. Go ahead.

19 DR. ZELTZER: I'm sorry. So again, I mean, as
20 I was hearing the data, there was nothing that stood
21 out in any major alarm way, except I couldn't get over
22 that the population in which the data were obtained

1 were not the usual -- not usual, but not the complex
2 population that this will be used in. So we don't have
3 safety data on the population that needs -- that the
4 indications are for, or that broader range.

5 That makes me concerned about the safety. And
6 obviously, you won't really know until it gets rolled
7 out in the real world, and you have a phase 4. But
8 still, the studies that were presented were in a
9 relatively healthy population overall, and the PCA, the
10 last study, we don't have enough data on who the
11 population was, the age, the risks, the other
12 medication. So it wasn't designed for a safety trial
13 in that sense.

14 So that's the part that makes me just a little
15 worried in terms of safety, even though the data
16 presented, as you presented it in that population,
17 seemed okay, relatively.

18 DR. ZACHAROFF: Dr. Alexander?

19 DR. ALEXANDER: Thank you. John Alexander
20 from Duke. Just to go walking down the four items, the
21 350 patients with the projected mean duration of
22 treatment seems largely arbitrary and historical, and

1 it's probably adequate. And I think that adding a few
2 hundred more relatively low-risk patients is unlikely
3 to add much.

4 Regarding hepatic safety, it doesn't seem to
5 be an issue to me. The only cases of concern come from
6 an uncontrolled, broad, relatively real-world study
7 with other potential explanations for hepatic injury.

8 The pattern of opioid related -- with that
9 I'll call respiratory and GI safety events -- seems to
10 favor oliceridine.

11 But whether this is a drug effect or a dose effect
12 isn't entirely clear to me. If you were to give a
13 lower dose of morphine, you would also have a pattern
14 of less respiratory and GI side effects, potentially.
15 So this dose equivalency is very important.

16 Then related to cardiac safety, I think we
17 need to conclude that there is a modest effect of
18 oliceridine on the QT interval. We see that in the
19 dedicated QT study, which is the purpose of doing it.
20 And if there's as much effect as our active control
21 that we typically use to pick out some QT effect,
22 really interestingly, this effect is delayed an hour

1 after the PK effect, and we don't right now know the
2 explanation for that disconnect between PK and peak QT
3 effect.

4 I personally don't find the APOLLO studies or
5 ATHENA particularly helpful. The APOLLO studies are
6 still a highly selected, low-risk population who
7 got -- I'll come back to this -- selected doses of
8 oliceridine, so I think dose is important. They had
9 EKGs at 1, 24, and 48 hours that were interpreted by
10 the sites. And site interpretations are likely to
11 increase noise. Even if going in the direction of
12 overestimating QT interval, this won't help detect a
13 modest signal if that's what our interest is in.

14 So given the issues related to efficacy and
15 safety and dose, I have concerns that higher doses will
16 be quite -- I expect that higher doses will be used in
17 practice in the broad range of patients who will get
18 this than were used in the QT study or the APOLLO
19 studies in higher-risk patients with more concomitant
20 QT prolonging medications, and that the cardiac safety
21 of these higher doses is unknown.

22 I don't know that there's a safety signal in

1 these higher-risk patients. I just don't think we
2 know. And a big part of why we don't know is this
3 disconnect between PK and the QT effect.

4 I'll just comment, in ATHENA, where there were
5 more real-world patients, patients received a mean of
6 19 milligrams with a range of point 0.9 to 224
7 milligrams over a 1 to 142 hours. And there were cases
8 of more QT prolongation in ATHENA, but it's an
9 uncontrolled population, so we don't know whether
10 that's due to oliceridine or one of the other
11 concomitant effects.

12 Then on the other hand related to QT still, we
13 have not seen significant ventricular arrhythmias in a
14 thousand or so patients who've gotten oliceridine, and
15 a large proportion of them more real world. And in
16 practice, many of these patients -- not all but many,
17 particularly the higher-risk patients, will be
18 monitored with telemetry.

19 Now, I don't have a great sense for what
20 proportion of patients getting all oliceridine would be
21 monitored, but at least the highest-risk patients
22 probably would be.

1 DR. ZACHAROFF: Thank you. Dr. Solga?

2 DR. SOLGA: I'm okay with the safety database,
3 the hepatic safety and the QT prolongation. The story
4 of the G-protein agonism was one of improvement in
5 respiratory safety and also nausea and vomiting. I
6 don't know what to make of the respiratory safety, and
7 I'm concerned that the impression that it's safer could
8 lead to less vigilance when it's actually used on
9 wards.

10 The most important way to find out if your
11 patient is breathing is to look at them. And it's
12 extremely important that folks respect the potential of
13 any of these medicines. And the impression that it's
14 safer without firm evidence that it is could actually
15 be counter-productive.

16 I am more impressed, however, by the study
17 drug's improvement in vomiting. I think that's been
18 somewhat under-discussed, and I add that as point E.
19 Vomiting is not so much a comfort issue. It really is
20 a safety issue. Particularly when folks are sedated,
21 vomiting could have devastating effects. And clearly,
22 there is a dose-related reduction in vomiting with

1 study drug compared to morphine. And even at 0.5,
2 there seemed to be less vomiting. So that does support
3 that hypothesis works.

4 DR. ZACHAROFF: Thank you. Mr. O'Brien?

5 MR. O'BRIEN: It's always when we get to these
6 questions that the real difficult charges come out.
7 It's interesting to me when we're asked for efficacy,
8 it's for substantial evidence, but when we get to
9 safety, it's adequate support; we sort of shift. And
10 when we're talking about efficacy, it's in comparison
11 to the placebo, but if we're talking about safety,
12 we're not talking about the placebo because in terms of
13 safety, no, we had adverse events. So compared to
14 placebo, if we're using the same thing as efficacy, no,
15 it's not safe from that perspective.

16 However, assuming that we're talking about
17 comparative here as opposed to when we're talking about
18 efficacy, my take-away is very much what I've heard
19 already. And as you know already, I was concerned with
20 the respiratory safety.

21 I thought it was very interesting listening to
22 my fellow patients and those that thankfully serve

1 those patients, we heard about itching and we heard
2 certainly about nausea and vomiting. I think that is a
3 very important issue in terms of the safety. But we
4 heard other things with constipation that really wasn't
5 explored. I don't know if that's safety and it's going
6 to save us from addiction. I don't think there's any
7 evidence for addiction in terms of being safe. We've
8 shown that it's not. It's going to be the same
9 actually for abuse and addiction. So from that safety
10 profile, I don't see any change to that. that.

11 Even from respiratory, with the FDA analysis,
12 which I go along with, I'm not quite -- as I explained
13 with my own particular situation and the patients that
14 I know, I don't see any evidence yet that the
15 hypothesis that there will be improved respiratory has
16 been shown, substantially for sure. So that's to me
17 the way -- it's safe, but no safer than anything else.

18 DR. ZACHAROFF: Dr. Kaye?

19 DR. KAYE: Alan Kaye from LSU in New Orleans.
20 I just wanted to make another comment. As we look at
21 this, we have to also consider drug-drug interactions.
22 There's a paper from 2012 by Nagel Anesthesiology

1 looking at non-cardiac adult patients for which they
2 measured QT prolongation. There are hundreds of drugs
3 listed that can cause QT prolongation.

4 So the point being, that study showed 1 in 25,
5 4 percent of people had significant QT prolongation.
6 So if you are throwing in another drug that would be
7 used in acute pain in all comers, you have to consider
8 drug-drug interactions.

9 I would say just globally, I agree with what
10 everyone has said. We have some data. Some of it's
11 pretty good; some of it is not as robust as we would
12 need to really feel comfortable. So it's kind of a
13 difficult challenge for us today.

14 DR. ZACHAROFF: Thank you. Dr. Alexander, did
15 you have anything else? No.

16 So just before I summarize, I just want to add
17 a couple of my own comments, and thanks for the good
18 discussion. In the real-world realm of things, a an
19 anesthesiologist, I certainly realize that the way I
20 look at things in an acute pain situation
21 post-operatively is that the pain management is sort of
22 a handoff, and a handoff, and a handoff.

1 When the patient leaves the operating room and
2 the anesthesiologist is going to make sure that there's
3 some level of analgesia there to get the patient to the
4 PACU. In the PACU, there's going to be some measures
5 that are taken to make sure that the patient's
6 comfortable and pharmacologic measures are going to be
7 taken. And then when the patient is discharged from
8 the PACU, and then they go up through the floor, then a
9 PCA might be implemented, or maybe the PCA might be
10 implemented before the patient is discharged from the
11 PACU.

12 Somebody earlier said something that really
13 struck a chord with me, and that is that the way the
14 dosing for this medication would be done is based on
15 what medications they had already been given. And I'm
16 not 100 percent confident that I know that if I loaded
17 a patient up with fentanyl before I left the operating
18 room, and then got a bunch of dilaudid in the recovery
19 room, and then we put them on the floor with this
20 medication, what that safety profile edge is.

21 The scenario that I'm describing to you, I
22 think as an anesthesiologists, we'll be able to nod and

1 say that's exactly what happens. It's multimodal
2 opioid analgesia, let alone multimodal analgesia in
3 total. So it may be outside the context of the
4 presentations today and the briefing materials, but
5 from a premise safety profile, I worry about what
6 happens on the front end when the patients have been
7 loaded with opioids, which they will have before this
8 medication is given to them, and what potential effect
9 from a drug-drug perspective that might have, because
10 we know there could be crossover respiratory depression
11 when dose meets dose and blood level meets blood level
12 after the fact.

13 I don't know what the answer to that question
14 is, and I didn't hear it discussed today. So that's my
15 perspective.

16 Just to summarize the discussion before we
17 take a 15-minute break, from the perspective of the
18 safety profile as we see posed in the question, my
19 summary would be that the general consensus is that
20 it's relatively safe overall, and that from a hepatic
21 perspective, it's probably similar to morphine or it
22 may be no more dangerous than morphine in the majority

1 of patients.

2 And there is insufficient data to really conclude one
3 way or the other based on what we've seen about whether
4 there's increased safety over morphine, especially
5 because of the confounding that we heard about with
6 respect to other medications given to the patient.

7 In increased doses maybe due to abuse or
8 medication error, it's likely to be as dangerous as
9 another opioid with respect to opioid-related side
10 effects? Agonist bias is definitely a good thing.
11 Looking at new ways and more specifically tailored
12 approaches is definitely a good thing from a safety
13 perspective, and I guess you have to start somewhere.

14 There was a sense that cold pressor tests and
15 things like that aren't necessarily real-world valuable
16 in terms of patient experiences. I guess from a safety
17 perspective, again, speaking as an anesthesiologist, we
18 measure end-tidal CO₂. We measure oxygen saturation in
19 real time. I'm not 100 percent sure myself about what
20 the testing that was done on young healthy volunteers
21 really has to do with hypercarbic drive.

22 We did hear some discussion about the fact

1 that 350 subjects weren't identified within the
2 therapeutic dose range for the maximum daily dose, but
3 I don't know that anybody around the table really has a
4 sense of the fact that if it was 250 versus 350 or 270,
5 whether that would really make a difference at the end
6 of the day.

7 We did hear discussion about the fact that
8 higher doses are likely -- or there is at least a sense
9 that higher doses may be likely to cause QT
10 prolongation, and at least there might be a modest
11 effect on QT prolongation. And we don't know, in the
12 context of other medications, what that might mean,
13 again, in a real-world perspective with patients being
14 on numerous medications.

15 With respect to the 27 milligrams a day, what
16 we heard was that there seemed to be a sense of at
17 least a few members of the panel that the data showed
18 the fact that it was safe for maximum to 27 milligrams
19 a day but not satisfaction that there was 40.

20 Just lastly with respect to the fact that
21 medications are good if they are decreasing incidence
22 of nausea and vomiting in post-operative situations.

1 Certainly, one of the patient populations they looked
2 at was a abdominoplasty. And I think I've actually
3 mentioned this before at one of these meetings, but
4 plastic surgeons don't like to see abdominoplasty
5 patients wretch and vomit. They specifically look the
6 anesthesiologist straight in the eye and say, "No
7 nausea, no vomiting."

8 (Laughter.)

9 DR. ZACHAROFF: So hopefully I was able to
10 capture the sense. If there's anything I left out,
11 please call it to my attention. If not, we're going to
12 take a 15-minute break and be back at 3:15 sharp to
13 address the two remaining questions, and ultimately
14 take our vote. Thank you.

15 (Whereupon, at 2:57 p.m., a recess was taken.)

16 DR. ZACHAROFF: Okay, everyone, welcome back.
17 We're going to proceed to the next discussion question,
18 which we'll see in front of us momentarily. Here we
19 go.

20 Considering the abuse potential of oliceridine
21 and its proposed use for acute pain in adults for whom
22 an intravenous opioid is warranted, please discuss any

1 concerns you have regarding the impact of this product,
2 if approved, on public health.

3 Before we move on to the discussion, I'll just
4 state as per protocol, if there are no questions or
5 comments concerning the word of this question, we'll
6 now open the floor to discussion.

7 Any concerns about the wording of the
8 question?

9 (No response.)

10 DR. ZACHAROFF: Okay. Discussion?
11 Dr. Higgins.

12 DR. HIGGINS: I guess my concern from a
13 patient perspective is that I don't see any superiority
14 of this medication over another for having abuse
15 deterrence. In comparison to -- the HAP studies that
16 were conducted by the FDA led me to see that there's no
17 difference between morphine in terms of likability and
18 other tests that were done through the HAP study. So I
19 have concerns about the abuse potential.

20 DR. ZACHAROFF: Thank you. Ms. Phillips?

21 MS. SHAW PHILLIPS: This really tags on to
22 Dr. Fischer's comments as well, and I think, again,

1 abuse potential from what we've seen that is like other
2 opioids -- and I agree it should be Scheduled II, but
3 patients or consumers might get the idea it's safer
4 from a respiratory depression standpoint.

5 So it's definitely not a safer drug to abuse.
6 There's no evidence to show that. And I think it's
7 presumption or word of mouth that it might be safer or
8 could lead to additional abuse or additional risk in
9 the hands of folks that might want to abuse it, but on
10 the whole, not a more abusable substance.

11 This is getting a little bit off the topic,
12 but I think the other issue in the opioid crisis is
13 drug shortages and drug availability. And I just got
14 another note from my health system saying, "We don't
15 have any PCA syringes that's going out to all the
16 physicians. We've got to manage things other ways,"
17 because we can't get enough opioids to treat patients
18 in hospitals because we're trying to decrease the
19 amount of available, and more and more is going to
20 abuse and back channels.

21 So I think we need to balance having drugs
22 that are effective and able to treat patients with

1 keeping them out of the hands of those that might abuse
2 them and do themselves ill.

3 DR. ZACHAROFF: Thank you. Dr. McCann?

4 DR. McCANN: I agree that the data shows that
5 the drug might be pleasurable much like morphine for a
6 number of patients, but I think it's going to be
7 relatively hard to divert the use of this drug since
8 it's only used in hospitals under supervision, and
9 there's just one formulation.

10 DR. ZACHAROFF: Thank you. Dr. Goudra?

11 DR. GOUDRA: Before I say anything, I have
12 couple of clarifications from Trevena. You guys don't
13 recommended it's used during and interoperatively,
14 right? During the procedure?

15 DR. VIOLIN: No, we have not studied
16 oliceridine interoperatively. In the APOLLO studies
17 and ATHENA, it was started after interoperative
18 anesthetics, including fentanyl and other opioids. So
19 it's never been studied as an interoperative
20 medication.

21 DR. GOUDRA: Just one more. Have you studied
22 it in terms of intranasal or transmucosal absorption?

1 DR. VIOLIN: No.

2 DR. GOUDRA: I know it's [indiscernible]
3 orally?

4 DR. VIOLIN: Yes. The oral availability is
5 almost zero. We've not --

6 DR. GOUDRA: And the reason for that?

7 DR. VIOLIN: First pass effect, so the
8 clearance is fast enough that it's metabolized and just
9 doesn't persist in the body if you take it orally. The
10 only thing we studied is intravenous administration.

11 DR. GOUDRA: Thank you.

12 Coming back to my comment, I think the entire
13 dosage is not selective enough, and that's what data
14 seems to say, at 3 times the clinical efficacy does, it
15 loses its selectivity. And as a result, especially
16 because it causes [indiscernible] and it is subective
17 to -- people can seek and use it for abuse purposes.
18 And over and above respiratory depression, we also now
19 have to face the prospect of patients suffering from
20 either hepatic or cardiac toxicity. So I think it is a
21 potential issue.

22 DR. ZACHAROFF: Thank you. Mr. O'Brien?

1 MR. O'BRIEN: It seems to me that there -- my
2 concern is it has been expressed in the sense that it's
3 not so much about the drug necessarily. It has the
4 same potential dangers as the other drugs, the other
5 opioids that are out there. It is about the perception
6 in terms of if you know it's going to do this, it's
7 going to do that, it's going to be safer than this
8 other drug. And because of the fact that it's
9 perceived as being safer, that may in fact create a
10 greater danger.

11 To the comment that it's going to be contained
12 and it's not out for public use, there have been many
13 other drugs that were supposed be contained that are
14 now out in the street for public use. So I'm not quite
15 sure that's something we can hold on to for a long
16 term. So yes, that is a concern that I have, that it
17 may be providing something that's going to create the
18 wrong image in a patient's mind that they can now take
19 the safely when they can't.

20 DR. ZACHAROFF: Dr. Terman?

21 DR. TERMAN: Yes. Thank you. So we're back
22 to this question, clearly the abuse potential is

1 greater than placebo, but the hope is that any new
2 medication is not going to add to the amount of opiates
3 that are being used, but to substitute for other
4 opiates if there's any benefit.

5 The abuse studies this morning, as you know, I
6 was very interested in that. And it seems like,
7 compared to morphine, that there's either equal or less
8 abuse potential in this drug. I think if there's a
9 public health issue, it's more likely to be what we
10 were just talking about in question 2, which is I have
11 no idea what the dose for PCA is.

12 I've been writing prescriptions for PCA for
13 30 years. I have no idea what the maximum amount that
14 FDA thinks we should be using per day of morphine. I
15 don't think that hydromorphone is approved through FDA
16 for PCA, and yet I do that every day. I certainly
17 don't know what the dose is that's approved.

18 So I think in terms of the indication
19 for -- well, not 0.5 but 0.35 -- and 0.38 might be
20 okay -- that is not the way it's going to -- once we
21 unleash this drug to the population, we are going to
22 see people that are taking a lot more than 24 or

1 30 milligrams. And the question is, is that something
2 I can live with or others; more importantly, patients
3 can live with.

4 DR. ZACHAROFF: Okay. Before we summarize
5 this, I will just throw in my own two cents, and that
6 is that I also consider abuse potential of people
7 within the healthcare setting that this drug might be
8 used. We know that people get their hands on drugs
9 that are kept in the hospital, and controlled setting
10 to me means it might be surgicenters or other places
11 where drugs might not necessarily be secured.

12 In my mind, agreeing with what we heard about
13 maybe the likelihood of equal or less regarding abuse
14 potential, I think that we should assume that many
15 people, this may be considered to be an opioid. And if
16 there's a perception that it's safer, then they might
17 be more likely to go into the drug cabinet and take it
18 out, and give it a whirl, and see what happens.

19 I think about that from an abuse potential
20 perspective as well as needing to consider risk outside
21 of just the patient and us when we're choosing a
22 certain medication now. We need to consider other

1 spheres that are moving around, like the community and
2 so on. So I figured I'd just throw that in.

3 So if there's no further comments for
4 discussion, to summarize, what I got out of hearing
5 your discussion points was that there is no superiority
6 likely for abuse deterrence. Schedule II is probably
7 appropriate for a medication like this. There is
8 concern that people might consider it to be safer to
9 abuse because of things they might hear. Availability,
10 as we heard, is definitely something that drives what
11 people abuse. If it's available, it's going to be
12 abused. And if there's perception that it's an opioid,
13 it's going to be abused.

14 On the other hand, we heard some thoughts
15 about the fact that it may be less likely to be
16 diverted if it's an institutional setting, but I don't
17 really know what the process will be for wasting a
18 medication like this. I assume it would be what the
19 same process is for wasting any other PCA or syringe
20 with it.

21 By and large, there was a sentiment that abuse
22 may definitely lead to respiratory depression based on

1 what we saw with the data, and the increased doses, and
2 the increased likelihood of adverse effects, including
3 possible hepatotoxicity, QT prolongation, and
4 respiratory depression.

5 If I missed anything you said, please let me
6 know.

7 (No response.)

8 DR. ZACHAROFF: No? Okay. Dr. Fischer?
9 Sorry.

10 DR. FISCHER: There's just one point to add on
11 that from a public health point of view -- and clearly
12 Trevena appropriately asked for this to be
13 Schedule II -- is something to make clear I would think
14 to clinicians, that for those patients we're managing
15 in inpatient settings with a history of opioid use
16 disorders and other problems, I'd be worried that there
17 will be a perception that this is a different kind of
18 opioid, and people will infer that it is somehow safer
19 for patients with that history, which it's not being
20 proposed to say that it is. But when we think about
21 public health concerns, that comes to mind; sort of an
22 outgrowth at the last point you made.

1 DR. ZACHAROFF: Very good point. So adding to
2 that, the perception is that there might be a
3 perception that this is safer for people who have a
4 history of an opioid use disorder. Thank you.

5 If there are no further questions or comments,
6 then we will now begin the voting process. The vote
7 is, do you recommend approval of the proposed dose of
8 oliceridine for the proposed indication of the
9 management of moderate to severe acute pain in adults
10 for whom an intravenous opioid is warranted?

11 After the vote, we'll have the ability to
12 discuss when you're giving us your rationale for the
13 way you voted. If you have feelings about what data
14 might be helpful to gather in the future, you'll have
15 the opportunity to answer that part of the question.

16 So the vote is that first sentence, do you
17 recommend approval of the proposed dose of oliceridine
18 for the proposed indication of the management of
19 moderate to severe acute pain in adults for whom an
20 intravenous opioid is warranted? Yes?

21 DR. FISCHER: When you say proposed dose, do
22 you mean both doses that are being proposed or are we

1 voting separately on each one?

2 DR. ZACHAROFF: We mean the proposed doses.

3 DR. FISCHER: Doses.

4 DR. ZACHAROFF: Yes, doses.

5 Yes, Mr. O'Brien?

6 MR. O'BRIEN: Again, I would just like
7 clarification on the question, recommend approval. Now
8 again, we're approving on efficacy and safety, or the
9 ratio of the relationship between efficacy and safety,
10 or -- because the third element is innovation, which is
11 another element, but we're not being asked for
12 innovation. We're being asked for efficacy and safety.

13 DR. HERTZ: This is Sharon Hertz. To clarify,
14 approval means this goes to market. So based on the
15 available data that you've heard about today, do you
16 think this should be approved for use commercially on
17 the market? However you think about it, I have a
18 regulatory standard for what is necessary, but that's
19 that risk-benefit that I described earlier.

20 So the question is, should this be approved so
21 that folks can use it in the appropriate setting at the
22 proposed dose?

1 DR. ZACHAROFF: Dr. Alexander?

2 DR. HERTZ: For the proposed indication.

3 DR. ZACHAROFF: Sorry.

4 DR. ALEXANDER: Just one more point of
5 clarification to follow up on Michael's question about
6 the dose. So we're talking about 1 to 2 milligrams
7 bolus up to a maximum of 40 milligrams a day, with the
8 2 PCA doses of point 0.1 and 0.35. Correct?

9 DR. ZACHAROFF: That's correct.

10 Okay. If there is no further discussion on
11 this, then we will now begin the voting process.
12 Please press the button on your microphone that
13 corresponds to your vote. You will have 20 seconds to
14 vote. Press the button firmly. After you've made your
15 selection, the light may continue to flash. And if
16 you're unsure of your vote or you wish to change your
17 vote, please press the corresponding button again
18 before the vote is closed.

19 (Voting.)

20 DR. ZACHAROFF: Everyone has voted. The vote
21 is now complete. Now that the vote's complete, let's
22 have a look at the vote.

1 DR. CHOI: For the record, we have 7, yes; 8,
2 no, and zero abstentions.

3 DR. ZACHAROFF: Now that the vote's complete,
4 we'll go around the table and have everyone who voted
5 state their name, vote, and if you want to, state the
6 reason why you voted as you did into the record. And
7 if you feel there's more data necessary, this would be
8 your opportunity to state that as well.

9 Let's start at this side of the room.
10 Mr. O'Brien?

11 MR. O'BRIEN: Okay. Well, clearly, I
12 struggled with this to be honest. It is Solomon's
13 sword. I would say that I did it primarily because I
14 think we need something different. We need a new
15 approach. And everything always has its first step,
16 and I see it as a first step.

17 Now, I say that saying that it's kind of taken
18 within a very small capsule here because I would then
19 want to say an add that we need the appropriate
20 controls. We need the appropriate labeling. We can't
21 let it go out here. I mean, there's an awful lot to
22 define what that means. I do have incredible concern

1 about a lot of issues here, so I was inclined to say
2 no.

3 But I also do think that we need to break this
4 epidemic that we have, and I don't think that the
5 approaches that we used so far is in fact going to
6 break it. And we have a community of people that I
7 deal with every day who was stuck between this world
8 where they have no other option than opioids. And
9 we're not giving them a good option. We need a better
10 option.

11 So thinking of that at the last second, I
12 changed my vote to a yes, and that's the honest truth.

13 DR. HIGGINS: Jennifer Higgins. I voted no,
14 largely for the reasons that I already mentioned. And
15 with respect to data needed, I will stress again the
16 need for demographic variability. I echo the concerns
17 of other people regarding the safety of the population
18 that was under study and look for people with
19 comorbidities or other kinds of disorders.

20 Again, I stress the need for older adult
21 research, and I always say that as a gerontologist.
22 But I applaud Trevena for doing some of that with their

1 studies, but I would like to see more of that. And
2 with respect to the open label, I would have liked to
3 have seen some control data.

4 DR. WARHOLAK: It's Terri Warholak, and I
5 voted no, although I really do like that this is an
6 innovative molecule and I recognize that better options
7 are needed for pain relief. I was also thinking that
8 specifically in the instances where there are allergies
9 to opioids, this might be a really great option.

10 So I really struggled with this decision, but
11 it's as stated; it's the proposed doses. And I don't
12 think the dose regimens have a positive risk-benefit
13 profile. I also worry, too, about the perception of
14 the decreased respiratory symptoms. And the reason for
15 that is as it was compared to morphine several times,
16 it wasn't compared in doses that were equivalent. It
17 was stated earlier that the equivalent morphine dose
18 was 5 to 1, and those weren't the doses that were all
19 presented.

20 So I would really worry that somehow people
21 would get the perception that it is more safe than
22 current opioids, and that might lead to downstream

1 problems. So for additional data, I would like to see
2 more data mostly on the doses that are proposed and
3 safety, as well as some studies on potential public
4 health risk.

5 DR. ALEXANDER: This is John Alexander from
6 Duke. I voted yes. Oliceridine is an effective
7 analgesic that probably has improved opioid-related
8 safety. The issue in sorting that out is all about
9 dose equivalency. I do have concerns about off-label
10 use, less about patient population than about regarding
11 dose. I think labeling should include some language
12 about that

13 The QT risk is probably modest and not unlike
14 a lot of other drugs that are used but has not been
15 completely characterized, and that fact should also be,
16 I believe, described in the label. We definitely need
17 more data, and probably controlled data. I really
18 don't think that single-arm uncontrolled data is going
19 to answer the questions we have in more real-world
20 settings where maybe broader ranges of dosing will be
21 used. And this probably would be a good opportunity to
22 collect additional QT data and further characterize

1 that QT risk.

2 DR. TERMAN: Yes. I'm Greg Terman from the
3 University of Washington, Seattle. I voted yes because
4 it'd be nice to have an IV opiate in this country that
5 isn't in short supply. No, I'm kidding.

6 (Laughter.)

7 DR. TERMAN: Although I couldn't help the dig.
8 The issue for me is that the pharmacokinetics
9 of this drug are attractive as someone who does this
10 kind of work full-time. Again, theoretically, for both
11 PK and this arrestin issue should be safer. I'm not
12 convinced that it is, but I am convinced that it's no
13 more dangerous unless it causes dangerous QT changes.
14 And there was nothing that I heard today that convinced
15 me of that. And the open-label trial, as was stated,
16 was all over the place in terms of dosage without
17 dangerous sequelae. So that's the reason I voted yes.

18 DR. KAYE: Alan Kaye from LSU. I voted no,
19 but it wouldn't have taken that much for me to vote
20 yes. I was concerned about subpopulations. I was
21 concerned about drug-drug interactions. And
22 specifically, in looking throughout the day to try to

1 understand what we have and how this would be helpful,
2 what I started focusing on was that morphine and
3 dilaudid, which are the principal medications we use
4 post-operatively, don't have associated QT effects.

5 That is one study, very focused, that would
6 turn me. It was a very difficult vote. Nonetheless,
7 without that information, I wouldn't want to create
8 problems for all the people in our country without that
9 information.

10 DR. McCANN: Mary Ellen McCann. I also voted
11 no, and actually for precisely the same reasons that
12 Alan Kaye did. I think if this drug's brought up in
13 another half a year or a year with more data, I would
14 be very, very happy to vote yes for this drug. I think
15 it hopefully will be a step forward. I think we just
16 don't have enough safety data to say that we're not
17 going to inadvertently harm people.

18 DR. SHOBEN: Abby Shoben. I also voted no and
19 sort of echo Dr. McCann's comment about wanting to vote
20 yes and hopefully soon we can because I think it does
21 have a lot of promise as an alternative to morphine in
22 this setting.

1 I voted no primarily due to this strict
2 interpretation of the question about proposed doses in
3 the 0.1 efficacy versus placebo and if that safety
4 profile is worth it. And I think I would like to see
5 comparison with a more equivalent dose of morphine, as
6 has been said, so that we're not approving a drug that
7 has a less favorable risk-benefit profile to morphine.

8 DR. ZELTZER: Lonnie Seltzer. I really
9 struggled with this vote. And clearly, as the vote
10 showed, probably a lot of people struggled. The only
11 thing that held me back from a yes vote was I felt
12 like, probably as part of this side of the table, that
13 it's almost ready for prime time but just not quite.
14 And knowing how it will be used in the real world with
15 likely sicker, more complex patients on more drugs, it
16 just needs a little more real-world safety studies, and
17 then I would be much more comfortable knowing how it
18 would be used.

19 I like the drug. I like the principle behind
20 the drug. It really was a struggle, but that's the
21 last little -- I don't think it will take much, but I
22 think it's just not quite ready yet.

1 DR. ZACHAROFF: This is Kevin Zacharoff. I
2 voted yes, and I voted yes because I agree with some of
3 the other people who voted yes that this is likely not
4 a more dangerous drug than morphine. I didn't see
5 anything today to indicate maybe that it was better
6 than morphine, but I certainly didn't feel that I saw
7 anything that made it more dangerous than morphine.

8 The open public hearing actually I found very
9 compelling. Many times in anesthesia, we hear people
10 talk about certain things that work and certain kinds
11 of things that they're doing. We heard the term "off
12 label." I worry that people might use a medication
13 like this in an off-label way, but the reality is that
14 people do and try, and we anesthesiologists do and try
15 all the time.

16 I didn't feel that it was superior to morphine
17 other than the fact that at least there was a possible
18 chance that in some patient populations, the adverse
19 effect profile might actually be lower.

20 DR. LITMAN: Ron Litman. I voted yes because
21 I asked myself what if there were no opioids, and this
22 was the first in class, would I want this for myself?

1 And the answer is yes, of course. That being said, I
2 do agree with everybody else on the panel, even those
3 that voted no.

4 The question then becomes, how much more data
5 do we need? And it would be wonderful to have just a
6 little bit more, as Dr. Zeltzer said, but thinking
7 about historically and other drugs, that kind of data
8 is rarely available. And the truth is that what we
9 agreed to or approve for labeling on the dose is not
10 real life as we talked about.

11 Whether we like it or not, the reality is that
12 most prescribers won't read the label, and it's legal
13 to do so. And once it's marketed, it's legal to use it
14 however we want, and that occurs. What's not legal is
15 for the company to market it for non-truthful purposes.
16 So I wonder if the FDA could ask for some kind of
17 language in the labeling that states something about
18 this drug has not been shown to be safer than morphine
19 or safer than traditional opioids until the truth of
20 that comes out.

21 So then in the end, I had to ask myself, as a
22 representative of the American people, is it better to

1 let them benefit from a drug that could possibly be
2 better, or do I withhold it from the American people
3 until we know that it's safe enough for them to use?
4 And in the end, I came down to the former.

5 I think that these kinds of issues work
6 themselves in phase 4 studies, in non-sponsored studies
7 over the years. As Dr. Terman alluded to before, we
8 take a chance, and it's something we grapple with if we
9 unleash this drug too early by mistake. But there's no
10 way we can know that today. There just isn't.

11 So overall, I had to look at their overall
12 safety profile on a couple thousand of patients that
13 have been exposed to it, the ones we knew about, and I
14 tended to vote yes.

15 DR. GOUDRA: Dr. Goudra from Penn medicine. I
16 did vote yes for many reasons. One, it doesn't
17 interact in metabolites, and I think that's a good
18 thing. You can use it in patients with renal failure,
19 where we can't use morphine for example.

20 It doesn't cause histamine release [ph];
21 that's good. I view every opioid as abuse problem, so
22 it's no exception. And yes, 0.1 is a problem or 0.35.

1 As Dr. Litman pointed out, we will figure out how to
2 use it once it is in the market. And drug
3 interactions, knowing almost 80 percent of the drug
4 undergoes hepatic microsomal enzyme metabolism. We
5 deal with that all the time. Long QT interval,
6 everybody gets Zofran almost, so that doesn't seem to
7 be a problem considering there are so many drugs for
8 long QT, which we use.

9 Yet, we do need much more selective G-protein
10 or something which doesn't have any beta arrestin
11 pathway activation. But I think it's a good beginning
12 and not having anything to kill this product at this
13 stage. Thank you.

14 DR. FISCHER: Mike Fischer from Boston. I
15 voted no. And many of the reasons have been said, so
16 I'll recap briefly. I agreed with many of the points
17 by the group around that corner of the table, who are
18 generally in agreement, concern about the lack of
19 difference from placebo of the lower dose and some of
20 the subpopulations, where the drug is likely to see its
21 highest use.

22 Then going to a couple of the points that were

1 made at the end to highlight the difference, like my
2 colleagues here, it was a tough decision. It feels
3 like it is very, very close. But I was given pause by
4 the disconnect from the overall theme. And actually,
5 Kevin, I took some of the comments a little
6 differently.

7 I felt like the theme that was coming out
8 overall was that here is a drug that is going to be the
9 answer to what we've been looking for. Here is
10 something that's much better. And when I went back and
11 took -- when I'm taking a hard look at the data, what I
12 think we have so far for the doses that are being
13 requested is something that is a little less effective
14 and a little safer. And that's not the message that is
15 coming across pretty strongly.

16 I take Dr. Litman's point that if there were
17 nothing available, perhaps this would be -- and we
18 needed something. But given how this is likely to be
19 used and the fact that phase 4 studies take a long time
20 and are hard to do, that disconnect gave me pause.

21 I feel like this is very, very close. If we
22 can get safety data at the doses at which this is

1 actually likely to be used, I think that would be
2 reassuring. And as one of the other panelists said, it
3 feels like it wouldn't need to be a very long time to
4 accumulate enough data to have us be reassured enough
5 that it's a safe alternative but also to release it out
6 there into the wild with a clear message about where
7 the relative safety and efficacy are.

8 MS. SHAW PHILLIPS: Marjorie Shaw Phillips. I
9 voted yes, the same kind of thing. I thought it was
10 better to vote yes with some qualifications rather than
11 no with some qualifications because I think it's
12 important that drugs in this class get on the market,
13 and there are some important benefits.

14 I think the important thing is safety or
15 relative safety at effective doses. And for individual
16 patients, it looks like it will totally be worth it
17 because we're really not talking about equivalent
18 doses. We're talking about doses that will meet
19 individual patient's needs.

20 The PK profile, the lack of active
21 metabolites, the relative safety at the steady state at
22 the proposed PCA doses and proposed bolus doses all

1 look good and are positive; the potential for less GI
2 side effects at those proposed doses as well. If I
3 were going to qualify it, one of the things I would
4 like to see is a statement that has not been adequately
5 studied at doses greater than 27 milligrams a day and
6 would be an opportunity to do that.

7 As far as further studies, I think looking at
8 it in opioid-tolerant patients and those that would
9 have higher opioid demands would be useful information.
10 And again, with the additional information in phase 3,
11 it would be worth the trade off for not getting an
12 important drug to market.

13 I do think also, as mentioned earlier by our
14 pharmacist colleague, that having an alternative for
15 patients who have morphine-related allergy or severe
16 side effects and tolerances is also important.

17 DR. SOLGA: Steve Solga. I voted no. Unlike
18 some others, I actually felt fairly firm with my no. I
19 felt like the efficacy versus placebo is there, but the
20 overall risk-benefit consideration to me was not.
21 Three doses of study drug were compared to a single
22 dose of morphine. If there was slightly less morphine

1 provided, I think all of the differences would go away,
2 and you'd basically have a me-too of a lower dose of
3 morphine, which does not meet the urgent unmet need and
4 is not innovative. In fact, it would potentially be
5 the opposite.

6 So I just want to be excited about these data,
7 but I found myself unable to be so.

8 In terms of what to do for a follow-up study,
9 I also found the public comments to be very important.
10 Many persons said they felt more awake. They were
11 talking. They were eating. They were moving. They
12 were engaged with their family. They moved their
13 bowels.

14 The summation of all of that means discharge.
15 So maybe a trial could be done, a randomized-controlled
16 trial, comparing time to discharge for a standard
17 operation where length of stay might be expected to be
18 24 hours. That could be an amalgam of both safety and
19 efficacy if study drug got folks out the door at
20 20 hours and morphine got them out the door at 30
21 hours, and ding, ding, ding, ding.

22 I get that idea from some years ago when FDA

1 looked at maintenance of remission of hepatic
2 encephalopathy with rifaxmin, encephalopathy endpoints
3 were simply too unreliable to study. There was no good
4 way to do that. So what FDA and sponsor agreed on was
5 rather than looking at encephalopathy endpoints, they
6 would simply look at time to readmission to the
7 hospital, time to readmission; very firm, very simple.
8 This could simply be the opposite, time to discharge.

9 DR. ZACHAROFF: Well, I want to thank you very
10 much for your good work today. Before we adjourn, I'm
11 just going to ask if there are any last comments from
12 the FDA.

13 DR. HERTZ: I'm not sure you made our job any
14 easier --

15 (Laughter.)

16 DR. HERTZ: -- but I think that you gave us a
17 lot to think about, and I appreciate the work you've
18 done today. Thank you.

19 **Adjournment**

20 DR. ZACHAROFF: Panel members, please take all
21 your personal belongings with you as this room is
22 cleaned at the end of each meeting day. Any materials

1 left on the table will be disposed of. Please also
2 remember to drop off your name badge at the
3 registration table on your way out so they may be
4 recycled, and we will now adjourn the meeting formally.
5 Thank you very much.

6 (Whereupon, at 3:54 p.m., the meeting was
7 adjourned.)
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