FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# JOINT MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEES

(AADPAC and DSaRM)

Open Session

Tuesday, June 7, 2016

9:30 a.m. to 2:54 p.m.

FDA White Oak Campus

White Oak Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:30 a.m.)

**Call to Order**

**Introduction of Committee**

DR. BROWN: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices, if you have not already done so. I would also like to identify the FDA press contact, Michael Felberbaum, who is in the back. Thank you, Michael.

My name is Raeford Brown. I'm the acting chairperson for today's meeting. I will now call the Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order.

We'll start by going around the table and introducing ourselves. We will start with the FDA to my left and go around the table.

DR. STAFFA: Good morning. My name is Judy Staffa. I'm the acting associate director for public health initiatives in the Office of

Surveillance and Epidemiology in CDER.

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

DR. FIELDS: Ellen Fields, deputy director in the same division.

DR. BATEMAN: Brian Bateman, associate professor of anesthesia, Harvard Medical School.

DR. BESCO: Kelly Besco, practicing pharmacist and medication safety officer for the Ohio Health Hospital System in Columbus, Ohio.

DR. WALSH: I'm Sharon Walsh. I'm a professor of behavioral science psychiatry from the College of Pharmaceutical Sciences at the University of Kentucky and the director of the Center on Drug and Alcohol Research.

DR. CHOUDHRY: My name is Niteesh Choudhry. I'm an internist and a health services researcher at Harvard Medical School and Brigham and Women's Hospital.

DR. MORRATO: Good morning. This is Elaine Morrato. I'm an epidemiologist and health services

researcher at the Colorado School of Public Health, where I'm also associate dean for public health practice.

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

DR. BEGANSKY: Stephanie Begansky. I'm the designated federal officer for today's meeting.

DR. BROWN: Rae Brown. I'm a pediatric anesthesiologist and professor of anesthesiology and pediatrics at the University of Kentucky.

DR. PERRONE: Good morning. I'm Jeanmarie Perrone. I'm an emergency physician, and medical toxicologist, and professor of emergency medicine and medical toxicology at the University of Pennsylvania.

DR. KAYE: Good morning. I am Alan Kaye, professor and chairman of anesthesia at LSU School of Medicine in New Orleans.

DR. EMALA: Charles Emala, professor of anesthesiology, vice chair for research, Columbia University, New York.

DR. McCANN: Mary Ellen McCann, associate professor at Harvard Medical School and Boston Children's in anesthesia.

DR. CAMPOPIANO: Melinda Campopiano, family physician, addiction medicine specialist. I'm a medical officer and branch chief for regulatory programs in the Division of Pharmacologic Therapies at the Substance Abuse Mental Health Services Administration.

DR. SPRINTZ: Hi. I'm Michael Sprintz. I'm an anesthesiologist, pain medicine specialist, and addiction medicine specialist, chief medical officer for Sprintz Center for Pain and Dependency in The Woodlands, Texas.

MS. CHAUHAN: Good morning, Cynthia Chauhan, patient representative.

DR. HIGGINS: Jennifer Higgins, consumer representative.

DR. GERHARD: Tobias Gerhard, pharmacoepidemiologist, associate professor of pharmacy at Rutgers University.

DR. WESSELMANN: Ursula Wesselmann. I'm at

the University of Alabama at Birmingham and I'm a professor of anesthesiology, neurology, and psychology.

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

DR. BROWN: Welcome to everyone. For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a general reminder, individuals will be allowed to speak into the record only if recognized by the Chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topics

at hand take place in the open forum of this meeting.

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

Now, I'll pass it to Lieutenant Commander Stephanie Begansky, who will read the conflict of interest statement.

**Conflict of Interest Statement**

DR. BEGANSKY: Thank you. Good morning. The Food and Drug Administration is convening today's Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting

members of these committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations. The following information on the status of these committees' compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not

so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

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

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

Today's agenda involves the discussion of new drug application 207975, hydrocodone bitartrate extended-release tablets, submitted by Teva Branded Pharmaceutical Products R&D, Incorporated, with the proposed indication of management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

The product is an extended-release formulation intended to have abuse-deterrent properties based on its physiochemical properties. The committees will be asked to discuss whether the data submitted by the applicant are sufficient to support labeling of the product with the properties expected to deter abuse.

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

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

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Joseph Herring is participating in this meeting as a non-voting industry representative, acting on

behalf of regulated industry. Dr. Herring's role at this meeting is to represent industry in general and not any particular company. Dr. Herring is employed by Merck and Company.

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

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

DR. BROWN: We will now proceed with the FDA's introductory remarks from Dr. Ellen Fields.

**FDA Introductory Remarks - Ellen Fields**

DR. FIELDS: Good morning. Dr. Brown, members of the Anesthesia and Analgesia Drugs Advisory Committee, members of the Drug Safety and

Risk Management Advisory Committee, and invited guests, we sincerely thank you for spending your valuable time at this meeting, where we will be discussing an application from Teva for a new extended-release tablet formulation of hydrocodone bitartrate, with the proposed trade name Ventrela ER.

If approved, Ventrela ER will have the same indication as the already approved extended-release, long-acting opioid analgesics; that is, the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Ventrela ER has been formulated with physical and chemical properties that are expected to deter oral, intranasal, and intravenous abuse. During this meeting, you will hear presentations from Teva on the development program for Ventrela ER and results of the in vitro physical and chemical manipulation studies and the human abuse potential studies they conducted to demonstrate

abuse-deterrent properties.

FDA will present drug utilization data for hydrocodone and other extended-release opioids, as well as the proposed labeling regarding the in vitro and in vivo abuse deterrence studies conducted by the applicant.

We are aware of the immense public health problem that exists in the United States today from the abuse of prescription opioids. As part of a larger effort across HHS, we at FDA have encouraged drug companies to develop novel interventions to reduce or, when possible, prevent this abuse.

To this end, we have supported the development of novel formulations through multiple interactions with both the pharmaceutical industry and the academic community. And in April 2015, we issued the guidance for industry, Abuse-Deterrent Opioids, which explains the agency's current thinking regarding studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, making recommendations about how these studies should be performed and

evaluated, and it discusses how to describe those studies and their implications in product labeling.

In response to the growing epidemic of opioid abuse, dependence, and overdose in the United States, the commissioner announced an opioid action plan in February of this year to take steps toward reducing the impact of opioid abuse on the public health.

As part of this plan, the agency has committed to work more closely with its advisory committees before making critical product and labeling decisions. As you may know, we are calling on all of you more often to fulfill this goal.

As we work to make opioid analgesics less desirable targets for abuse, we cannot forget that the underlying purpose of these products is the management of pain in patients for which other alternatives are inadequate, and opioid analgesics remain an important component of their pain management.

The greater amount of opioid available in

many extended-release opioid analgesics relative to immediate-release products is associated with greater risk for overdose and death, but also makes these products a desirable target for those seeking to abuse opioids.

However, immediate-release opioids are also abused and the development of abuse-deterrent immediate-release formulations that can reduce opioid abuse is also an important public health goal.

While the most common route of abuse for opioids is oral, the risk for infection and overdose associated with intravenous or nasal routes make these routes of abuse important targets for abuse-deterrent properties.

With every new product, we weigh the risks and benefits. With new abuse-deterrent formulations, we are also watchful for any evidence that the product results in a new or increased safety risk for patients who take the product as directed, as discussed at an advisory committee last September, and for any evidence that by

deterring abuse of one route of administration, the new product may shift abuse to a riskier route; for example, deterring oral abuse, but inadvertently making nasal or IV abuse more attractive.

There are currently six approved extended-release opioid products with abuse-deterrent properties and we are watching the post-marketing data closely for any signs of unintended problems associated with these products.

Today, you will be asked to discuss whether the applicant has demonstrated abuse-deterrent properties for their product that would support labeling the routes of abuse for which abuse-deterrent properties have been demonstrated and whether Ventrela ER should be approved.

These are clearly difficult questions for which there are no easy answers. We are asking that you provide your expertise, your experience, and your best insights in order to help us find a reasonable and responsible path forward. Your advice and recommendations will be essential in assisting us with addressing this complex and

critical public health concern.

We are grateful that you have agreed to join us and look forward to this important discussion.

DR. BROWN: Thank you, Dr. Fields.

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

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of the meeting. Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of

financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Teva's presentations.

**Applicant Presentation - Douglas Harnish**

DR. HARNISH: Good morning. I'm Douglas Harnish, senior director and regulatory affairs head of pain and migraine at Teva Pharmaceuticals. We'd like to thank the FDA and the advisory committee members for your time today to discuss Teva's NDA for Ventrela ER.

Ventrela ER is a hydrocodone bitartrate extended-release tablet intended for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

This indication matches that of other extended-release opioid products. Ventrela ER is a single-entity hydrocodone product that's free of acetaminophen, that is dosed every 12 hours. It comes in various strengths from 15 to 90

milligrams.

Ventrela ER tablets consist of a novel abuse-deterrent formulation using three complimentary layers with Teva's abuse-deterrent technology. The novel three-layer, extended-release formulation used for Ventrela needs to produce consistent drug delivery to provide analgesia over a 12-hour period, but it still needs to act as a barrier to resist drug extraction via the most common routes of manipulation used for extended-release hydrocodone products.

As with any abuse-deterrent formulation, the expectation is to deter abuse, but not fully prevent it.

The Ventrela program was conducted in close collaboration with the FDA. We had numerous interactions with the FDA concerning both the design and breadth of the in vitro manipulation and clinical studies to adequately evaluate the abuse-deterrent properties of Ventrela ER.

For the confirmation of analgesic efficacy, a phase 3 study was conducted in chronic pain

patients. Ventrela ER met its primary phase 3 endpoint of worse pain intensity, or WPI, demonstrating statistically significant pain reduction compared to placebo, with a safety profile consistent with that of other ER opioids. The Ventrela abuse-deterrent program does align with FDA guidance that was first proposed in 2013 and finalized in April of 2015 to evaluate abuse-deterrent features.

The goal of the abuse-deterrent program is to test the formulation to failure by assessing various physical and chemical manipulations, as well as assessing relevant routes of abuse. For extended-release formulation, the intent is to be resistant to conversion to an immediate-release formulation upon manipulation.

Therefore, both Cmax and Tmax become very important variables to monitor, because as with any extended-release formulation, drug will continue to release over time.

Our presentation today will demonstrate that Ventrela ER provides significant barriers to deter

abuse. We will show Category 1 studies demonstrating that Ventrela has physical and chemical properties that are expected to deter abuse via the most common routes.

Our Category 2 oral and intranasal PK studies demonstrated that the abuse-deterrent properties of Ventrela limit the extent and rate of rise of drug concentration after manipulation.

Finally, our Category 3 studies confirm that manipulated Ventrela has reduced drug liking when administered via the oral and intranasal routes. Overall, we believe these data support labeling that Ventrela ER has properties expected to deter abuse.

Teva is also committed to responsible pain management, while protecting the overall public health. If approved, Teva will be working within the framework of the FDA's opioid action plan, including joining the ongoing and expanded post-marketing requirements for long-acting opioids, inclusive of a Category 4 real-world abuse study.

We'll be participating in the updated REMS

program, and we'll be supporting safer prescribing and use of opioids to reduce the impact of opioid abuse, while providing effective analgesics in the treatment of chronic pain.

With this in mind, let's review today's agenda. Dr. Charles Argoff, a neurologist and globally recognized pain expert, will discuss the need for effective, extended-release opioids for the treatment of chronic pain that also deter the most common forms of misuse and abuse.

Next, Dr. Richard Malamut will present the clinical efficacy and safety data.

Then, Dr. Derek Moe will present our Category 1 abuse deterrence studies.

Dr. Lynn Webster, a globally recognized pain management and opioid abuse expert, will discuss our Categories 2 and 3 abuse deterrence studies.

Finally, Dr. Malamut will conclude with a summary and a discussion of the overall benefit-risk. All external experts have been compensated for their time and travel expenses to today's meeting. We are also joined today by additional

experts available to respond to your questions.

I will now invite Dr. Argoff to discuss his perspective on the medical need for abuse-deterrent technologies.

**Applicant Presentation - Charles Argoff**

DR. ARGOFF: Good morning. My name is Charles Argoff. I'm a professor of neurology at Albany Medical College and director of the Comprehensive Pain Center at Albany Medical Center. Thank you for the opportunity to address the patient need for extended-release opioids that deter abuse.

Opioid therapy has proven benefits for patients with chronic pain disorders. As their use has increased for the millions of people who suffer from chronic pain, so has the abuse of opioid analgesics. We recognize that our patients need access to opioid analgesics to optimally treat their chronic pain conditions.

We as prescribers recognize that we must work jointly with public health authorities to manage risk, while maintaining availability of this

important option for prescribers and patients in the management of chronic pain.

The Institute of Medicine issued a report on managing pain in the United States, emphasizing that millions of U.S. adults experience chronic pain every day. This includes conditions such as low back pain, osteoarthritis, and cancer pain.

No two people experiencing chronic pain respond equally well to the same regiment. When following an opioid-sparing approach, many patients, regrettably, do not find sufficient relief. For these patients, chronic opioid therapy may offer substantial long-term benefit and improved quality of life.

Abuse and diversion of opioids are a well recognized public health challenge. Since 1999, the number of deaths associated with opioids has increased nearly fourfold. The CDC has reported that in 2014, more than 14,000 Americans died from overdose involving prescription opioids.

The Drug Abuse Warning Network estimated that more than 420,000 emergency department visits

were related to the misuse or abuse of narcotic pain relievers in 2011, the most recent year for which data are available.

Opioid analgesic abuse costs payers more than $72 billion a year in direct healthcare costs. A huge challenge facing all of us is providing patients with appropriate access to these effective analgesic agents without making the problem of prescription opioid abuse worse.

The availability and use of abuse-deterrent formulations are one key step to confronting this public health issue. They are part of a larger solution to address abuse of prescription opioid analgesics. Increasing access to these abuse-deterrent formulations is pivotal in helping clinicians more safely manage their patients who benefit from chronic opioid therapy.

Many opioid abusers try to manipulate extended-release opioid formulations to allow for quicker release of more drug. This so-called dose dumping results in a pharmacokinetic profile more consistent with an IR formulation. This PK profile

of higher Cmax and shorter Tmax is linked to greater euphoria, drug liking, and abuse liability.

In an attempt to limit this behavior, some abuse-deterrent products rely on hardness as a physical barrier to resist reductions in particle size and, therefore, deter abuse. Literature suggests that the majority of abusers will not spend longer than 10 minutes manipulating extended-release opioids.

The goal of abuse-deterrent opioids is to curb abuse for these casual abusers. Of course, all abuse-deterrent opioids can be defeated with enough time and effort. After all, the products have to be bioavailable for patients.

Knowing the most common physical and chemical manipulations employed by abusers has helped develop formulations that better resist product release and extraction. Category 1 through 3 studies evaluate this potential.

Extended-release formulations are more likely to be manipulated and either swallowed, used intranasally, or injected. The oral route is by

far the most common route of abuse for ER opioids.

We know that abusers seek methods to defeat the abuse-deterrent properties via manipulation and extraction. Therefore, as abusers learn to circumvent existing abuse-deterrent formulations, there is an urgent need for improved abuse-deterrent opioids. Currently, the FDA and other health authorities are focused on development of abuse-deterrent opioids to protect the public health.

Increasing access to these formulations is key in helping clinicians more safely manage their patients who benefit from chronic opioid therapy. I recognize the value of extended-release opioids to treat appropriate patients in my practice. I see the importance of safer abuse-deterrent opioid formulations for chronic pain when other pain management options have not provided meaningful relief.

As a practicing pain specialist who also contributes to the medical literature in this field, the availability of additional abuse-

deterrent options is imperative for my ability to help my patients.

Thank you. I'll now turn the lectern to Dr. Malamut to discuss the phase 3 efficacy and safety results.

**Applicant Presentation - Richard Malamut**

DR. MALAMUT: Thank you, Dr. Argoff. I'm Dr. Richard Malamut, senior vice president for global clinical development at Teva. I will be reviewing efficacy and safety findings that support the NDA for Ventrela ER. In part, efficacy of Ventrela ER is supported by the agency's previous finding of efficacy for hydrocodone from the reference drug Vicoprofen.

I would now like to review the data from our pivotal phase 3 study, 3103. Study 3103 used a multi-center, double-blind, placebo-controlled, randomized-withdrawal design. This phase 3 study design aligns with that utilized for other extended-release opioid analgesics approved for the treatment of chronic pain.

As part of our considerations for the design

of study 3103, we included learnings from the phase 3 efficacy study, 3079, which did not demonstrate statistical significance for its primary endpoint. We enrolled adult patients who suffered from moderate to severe chronic low back pain for at least three months prior to screening.

Patients were randomized to doses of 30 to 90 milligrams every 12 hours, with a 15-milligram dose utilized only for titration purposes. Rescue medication was limited to immediate-release opioids at a maximum of 60 milligrams hydrocodone, 3900 milligrams acetaminophen during the double-blind portion of the study. This ensured adequate analgesia for these patients who suffer with severe pain and, also, minimize the rate of discontinuation.

The study design was reviewed with the FDA at our end-of-phase-2 meeting. Once enrolled in the screening, patients began an open-label titration period lasting up to six weeks. During this titration period, each patient's individualized optimal dose of Ventrela ER of at

least 30 milligrams every 12 hours was determined based upon efficacy and tolerability.

During the open-label titration period, the mean worst pain intensity, on an 11-point numerical rating scale, decreased by 3.72 points; and, the mean average pain intensity, on an 11-point numerical rating scale, decreased by 2.95 points.

After the titration period, patients were randomized 1:1 to receive either their optimal dose of Ventrela ER or a matched placebo. This dose was then maintained for weeks 3 through 12. In order to both reduce withdrawal symptoms and mitigate the potential for pain rebound in patients to be randomized to placebo, a step-wise double-blind tapering schedule was used during the first two weeks of the double-blind study.

The primary efficacy measurement of average worst pain intensity was collected during week 12. Patients were followed for an additional four weeks to collect safety data if they did not continue into the open-label study 3104.

The primary efficacy endpoint in study 3103

was the change from pre-randomization baseline to week 12 in the weekly average worst pain intensity. The primary analysis assessed intent to treat, with multiple imputation of missing data. The primary endpoint of the study was met.

As seen here, at 12 weeks, patients in the Ventrela ER group showed a statistically significant lower increase in pain scores compared with placebo. Sensitivity analyses were conducted and all were significant, showing that the results of the primary efficacy analysis were robust and not sensitive to method of imputation or potential confounding factors.

Our first secondary endpoint, based on average pain intensity, also demonstrated a statistically significant treatment effect, as seen here. This finding further confirmed the efficacy of Ventrela ER in the reduction of chronic pain.

The next secondary endpoint, time to loss of efficacy, was lower in the Ventrela ER group, but not statistically significant, with a p value of 0.059. Therefore, all subsequent secondary

endpoints were deemed not statistically significant on the basis of the hierarchical method to control for type 1 error rate due to multiple endpoints.

Now, let's move on to our safety data. In part, the safety of Ventrela ER is supported by the agency's previous findings of safety for hydrocodone from the reference drug Vicoprofen.

In study 3103, no unexpected safety concerns were identified for Ventrela ER as compared to placebo, and the adverse events collected were consistent with those seen in other clinical studies of extended-release opioids.

The most common AEs reported with Ventrela ER were constipation and nausea. Safety was also assessed by pooling data from 1,176 patients across all phase 3 studies, including long-term, open-label extension studies where patients were treated for as long as 12 months.

The safety profile in this broader cohort was consistent with what we see with other extended-release opioids, and no new safety concerns were observed with this longer duration of

therapy.

A total of 1,176 patients received at least one dose of Ventrela ER, with an overall exposure of 412.12 patient years and a maximum exposure of 15.8 months. 363 patients were treated with Ventrela ER for at least six months and of those, 197 patients were treated for at least 12 months.

In summary, the phase 3 study 3103 supports efficacy of Ventrela ER for patients with chronic pain. The primary efficacy endpoint was met, and the results were supported by multiple sensitivity analyses.

Finally, the safety profile was consistent with published data from placebo-controlled studies assessed or other extended-release opioid products.

Thank you. I will now turn the lectern to Dr. Derek Moe to discuss our Category 1 abuse-deterrent data.

**Applicant Presentation - Derek Moe**

DR. MOE: Good morning. My name is Derek Moe and I am vice-president of drug delivery technologies for Teva. I am pleased to begin the

review of Teva's development activities that characterize the abuse-deterrent properties of Ventrela ER.

Ventrela was developed in close collaboration with the FDA over a period of four years, and our studies implemented FDA advice. Ventrela is designed to retain its extended-release properties following the most likely methods of chemical and physical manipulation.

We tested Ventrela against comparators containing hydrocodone, including immediate-release Vicoprofen, hydrocodone API, and Zohydro ER, once it was commercially available. Our goal is to retain extended-release characteristics following manipulation and making the product less attractive to abusers.

I will now take you through the Category 1 studies that tested Ventrela against physical and chemical manipulations meant to mimic the most common routes of abuse. The Category 1 studies are specifically designed to push the formulation to the limits. Many of these tests are beyond what a

recreational user would attempt.

Based on the in vitro, pharmacokinetics, and human abuse potential studies, Ventrela is expected to provide abuse deterrence. When compared to a non-abuse-deterrent opioid formulation, our extensive studies found that Ventrela retains extended-release properties following chemical and physical manipulation.

As a result, Ventrela has a lower abuse potential via the two major routes of abuse, which are oral and intranasal ingestion. In addition, extensive in vitro studies demonstrate that Ventrela provides a significant barrier to abuse via injection.

Advanced isolation methods that result in the greatest amount of extraction also result in low drug purity. This is an important consideration for IV abuse, since additional material will be injected along with the active ingredient.

Moving now to a review of Category 1 laboratory-based, in vitro testing and results.

Our studies ranged from simple, physical manipulations that casual abusers might use to complex techniques of a sophisticated abuser.

The tests were based on a wide range of sources to ensure we were evaluating Ventrela against methods that abusers use in the real world. This means we scoured internet chat rooms, consulted experts in the field, and acted on information from the FDA.

In addition to these real-world methods, we also tested the limits of the formulation by using combinations of conditions involving high heat, extreme cold, vigorous agitation, and a variety of solvents. These conditions are not typically used by the majority of abusers, but are included here to characterize the formulation's abuse-deterrent profile.

This resulted in 844 independent experiments. In order to determine the 95 percent confidence interval, each individual experiment was repeated multiple times, which produced 3,798 individual results.

Tests included efforts to break the formulation by cutting, crushing, milling, and grinding the tablets in attempts to increase extraction rate. We performed extraction in a variety of solvents, at a range of temperatures and mixing conditions. We also performed chemical extraction and more exotic multi-step chemical extraction. We performed simulated oral ingestion, simulated intranasal, and IV extraction.

Now, let's focus on each of these sections one at a time, starting with the physical manipulations. We performed screening studies using 15 tools that represent different mechanisms of particle size reduction.

This includes tools that work by milling, cutting, grinding, or crushing, really any physical mechanism an abuser might attempt to break down an extended-release formulation. We ultimately selected five tools for our Category 1 studies that represented the various mechanisms of destruction and were worst case for each type.

Since the body of data is so large and four

of the tools gave similar results, in the next series of slides, we will show extraction data using two manipulation tools. We show Tool E because it is a worst-case tool that would only be used by dedicated abusers due to time, effort, and impracticality of use.

We will show Tool A because it has a similar release rate as other tools on Ventrela. Also, it is feasible to manipulate Zohydro ER with Tool A, allowing a head-to-head comparison across all tests versus a non-abuse-deterrent, 12-hour hydrocodone product.

The rate of drug release was compared between manipulated Ventrela and manipulated Zohydro using dissolution over six hours. For simulated oral ingestion, the first 30 minutes have been cited in draft, abuse-deterrent generic guidance from FDA as the critical time period that would indicate loss of extended-release properties if 80 percent or more of drug is released.

We'll be using this threshold when we discuss simulated oral ingestion studies. In our

simulated oral ingestion dissolution testing, Ventrela maintained extended-release properties after manipulation, and the release profile was well below the 80 percent threshold at 30 minutes that I just mentioned.

For manipulated Ventrela, we saw release profiles of 9 percent with Tool A and 44 percent release with Tool E at 30 minutes. This compares to 97 percent released for Zohydro. After two hours, the release rate for Ventrela increased to 35 and 66 percent compared to 99 percent released drug for Zohydro. These results are particularly relevant since the oral route of administration is the most common route of abuse, as Dr. Argoff mentioned earlier.

Moving now to an overview of simulated intranasal and IV evaluations, here is a picture of a Ventrela tablet that has been manipulated and dispersed in 10 milliliters of fluid. As you can see, when the vial is turned upside down, the formulation will stick to the bottom of the vial. This image helps to demonstrate how viscous the

product can become and the challenges it presents when trying to insufflate the product or dissolve in small volumes of liquid for IV injection.

Moving now to the data for simulated intranasal extraction. In simulated intranasal insufflation tests, we found that very little drug from Ventrela was released in all conditions compared to Zohydro. Here, you see results from Ventrela and Zohydro, both manipulated with the tools we have discussed.

Manipulated product was placed in fluid at various times. At the 10-minute point, Ventrela had a release profile of 1 percent with Tool A and 12 percent with Tool E. This compares to 89 percent of drug released from manipulated Zohydro at the same 10-minute mark.

The release rates increased slightly at the 30-minute mark for both Ventrela and Zohydro.

We also conducted evaluations of injectability and syringeability, demonstrating that Ventrela has the potential to deter the IV route of abuse.

Ventrela was analyzed for IV injection in two ways; first, as an intact tablet in solution, which resulted in syringeable liquid, but little active drug in the injection; and, second, after manipulation with several tools and mixing, the resulting solution was a difficult-to-syringe viscous material with little drug.

Ventrela exhibited a significant barrier to extraction of hydrocodone for IV abuse, even when using the most destructive tool, compared to Zohydro. The times represented in this experiment reflect how long an abuser might spend to prepare a product for an IV injection.

While manipulated Ventrela resisted release of hydrocodone in the small volumes required for injection, with 5 and 20 percent of drug release, there was more than an 80 percent extraction of hydrocodone from manipulated Zohydro within one minute. These extraction rates were similar when tested after five minutes.

Next, we conducted extraction studies to evaluate the rate of drug release in common aqueous

ingestible fluids. We also used advanced solvents in an effort to extract pure drug. These solvents have a range of polarity and pH.

An abuser will use common aqueous solvents to produce a drug solution intended to be consumed orally. Conversely, they would use advanced solvents to extract and isolate pure drug powder that would typically be used for IV abuse. As a result, purity becomes important when examining advanced solvents.

The studies investigated the influence of exposure times, temperature, and agitation on manipulated Ventrela and Zohydro. Here, we compare extraction of manipulated Ventrela versus manipulated Zohydro using two different liquids.

The chart shows the amount of drug dissolved and the time spent to achieve this value. Shown here are the results when Ventrela is manipulated with Tool A and Tool E prior to mixing. At 30 minutes, we see 8 to 29 percent extracted from Ventrela compared to 78 to 97 percent with Zohydro.

Ventrela ER was tested in Category 1 studies

to the point of failure, so it's not surprising that we found certain combinations of stress conditions that overcame the abuse-deterrent properties. As shown earlier, Ventrela was not defeated in the simulated oral ingestion studies with manipulated powder.

However, in the chemical extraction studies, we found a process where more than 80 percent of drug can be released in 30 minutes. This involved, first, manipulating Ventrela and then subjecting it to a specific combination of stressors applied simultaneously.

This is not unexpected as abuse-deterrent formulations are abuse deterrent, not abuse proof. Ultimately, these are medications that need to release the drug in order to provide relief for chronic pain.

Data is shown here that Ventrela exhibits a greater barrier to hydrocodone extraction with advanced solvents than Zohydro. When an abuser performs an advanced solvent extraction, they isolate a mass of material that consists of API,

release-controlling polymers, tablet excipients, and residual solvents.

The percent purity represents the amount of the mass of powder that is actually hydrocodone. While both Ventrela and Zohydro show near-complete chemical extraction when isolated as a powder, the purity for Ventrela was much lower than Zohydro.

Here, you see on the Y-axis, this is the percent of drug purity achieved through extraction. On the X-axis, we see the results of Ventrela and Zohydro when extracted in five different solvents. For each solvent, we tested Ventrela tablets, manipulated with the two tools we've been discussing, in blue, compared to the manipulated Zohydro, in yellow.

Ventrela saw purity rates ranging from a low of 3 percent to a high of 18 percent. In comparison, the purity levels extracted for Zohydro range from 26 to 94 percent.

Taking it to the next step, we conducted several multi-step chemical extraction tests. This type of test is used by only the most dedicated and

chemistry-savvy individuals in an attempt to isolate pure drug. Here, we see a similar trend with respect to purity. In addition, the extraction amount is shown below each bar, revealing incomplete extraction.

The results show Ventrela formulations exhibited a greater barrier to hydrocodone extraction with a multi-step method than Zohydro. While extraction rates ranged from 26 to 78 percent for Ventrela, the purity of drug substance extracted was low, from 10 to 42 percent. This is likely due to significant amounts of extracted polymer entrapped in the resulting powder. For Zohydro, extraction rates ranged from 46 to 95 percent and the purity was 72 to 81 percent.

In summary, our Category 1 in vitro studies demonstrated that Ventrela ER maintained its extended-release profile, even after applying techniques, methods, and practices known to be used for abuse.

These studies are specifically designed to push the formulation to the limit. Under all but

the most extreme conditions, Ventrela retains extended-release properties following chemical and physical manipulation compared to a non-abuse-deterrent opioid formulation.

I am now pleased to introduce Dr. Lynn Webster, who will review our Category 2 and 3 studies.

**Applicant Presentation - Lynn Webster**

DR. WEBSTER: Thank you, Derek. Good morning, everyone. I'm Lynn Webster, vice-president of scientific affairs at PRA Health Sciences in Salt Lake City. I was the principal investigator on some of the Category 2 and 3 studies. I also have a keen interest in opioid abuse and misuse and have published extensively in this field.

I'll be presenting the results of the Category 2 and 3 studies. As mentioned earlier, Ventrela is designed to retain significant extended-release properties following manipulation, limiting the rate and extent of rise in drug concentration.

In the Category 2 studies, we evaluated the PK profiles of manipulated and intact Ventrela in two oral studies and one intranasal study. Prior to discussing the Category 2 results, let me first begin with a requirement for any extended-release product, and that is evaluating the potential for dose dumping when taken with alcohol.

Here are PK profiles when intact Ventrela is taken with water, 4 percent, 20 percent, and 40 percent alcohol solutions. For alcohol, these proofs generally represent the equivalent of beer, fortified wine, and hard alcohol.

As you can see, the PK profile of Ventrela was not affected by ingesting alcohol. However, Ventrela, like all opioids, should not be taken with alcohol to the potential safety risk of the additive CNS depression.

Before we move into the Category 2 PK profiles after manipulation for oral and intranasal routes, I'd like to take a moment to introduce the relationship between pharmacokinetics and drug liking.

The FDA guidance recognizes the rate and extent of rise in drug concentration as important contributors to abuse potential. This can be measured based on assessments of early exposure, which may be most interesting to abusers.

These parameters include early plasma concentration or partial area under the curve, as well as traditional parameters such as Cmax and Tmax. Let me show you what this means.

The blue line represents an example of a typical PK profile of an extended-release formulation. Following a successful manipulation, a non-abuse-deterrent extended-release formulation can be converted into an immediate release of the drug, represented by the red line.

As you would expect, the earlier Tmax and the higher Cmax, the more abusers tend to like the product.

Now, let's look at the PK of Ventrela if an abuser attempted to overcome the abuse deterrence.

The first oral Category 2 PK study, study 1079, characterized the PK of intact and

manipulated Ventrela compared to Vicoprofen. This study was a randomized, open-label, crossover design in healthy volunteers. The dark blue line represents the PK profile for intact Ventrela ER.

Consistent with its ER properties, the intact Ventrela showed a late Tmax of about seven hours and a low Cmax. In comparison, both manipulated and intact immediate-release Vicoprofen had dramatically higher Cmax and earlier Tmax, shown in red and yellow.

Conversely, the Cmax for manipulated Ventrela, shown in light blue, was lower than the intact or crushed IR product. The Tmax for manipulated Ventrela was also later than it was for the intact and crushed Vicoprofen.

The next study, study 1085, was a combined Category 2 and 3 oral, randomized, double-blind, placebo-controlled, crossover study using manipulated Ventrela compared with intact Ventrela and hydrocodone API as the control. Following administration of intact Ventrela, again, Cmax remained low, with a Tmax of about seven hours.

As with the previous study, hydrocodone plasma levels, in red, rose rapidly to a higher Cmax following administration of hydrocodone API. In contrast, Ventrela retained significant extended-release properties even when manipulated. Peak concentrations for manipulated Ventrela were also lower as compared to hydrocodone API. The Tmax for manipulated Ventrela was much later, occurring at four hours post-dose.

The third study, study 132, was a combined Category 2 and 3 randomized, double-blind, placebo-controlled, crossover intranasal study. Here, manipulated Ventrela was compared to hydrocodone API, as well as Zohydro ER, which was a non-abuse-deterrent, extended-release hydrocodone product that became available just prior to the start of the study.

Consistent with the oral studies, intact Ventrela administered orally had an extended-release profile and both comparators, hydrocodone API and manipulated Zohydro ER, showed an immediate-release profile. We, again, see that

manipulated Ventrela administered intranasally had a slower rise to a lower Cmax and a longer Tmax, maintaining extended-release properties following manipulation.

In summary, Category 2 PK results demonstrate that Ventrela retains ER properties following manipulation, as would be suggested by the Category 1 studies. When Ventrela is manipulated for oral or intranasal administration, the extended-release properties result in lower Cmax and later Tmax.

This resulted in lower early hydrocodone exposure as compared to non-abuse-deterrent controls and immediate-release formulations. The rate and extent of rise in drug concentration are important contributors to abuse potential.

With this in mind, let me now present the Category 3 human abuse potential results. There were two Category 3 human abuse potential studies, an oral and an intranasal study. Before presenting the results, I'd like to note that the study designs were consistent with regulatory guidance

and accepted practice for abuse-deterrent studies.

They were randomized, double-blind, placebo-controlled, crossover studies in non-dependent, recreational drug abusers. Both studies used Emax, or peak score, as the primary endpoint. The bipolar visual analog scale of at-the-moment drug liking was used, as recommended in the FDA guidance.

An additional primary endpoint of overall drug liking was used in the intranasal study. A number of secondary PD endpoints were also collected in both trials. These included willingness to take the drug again and good effects, in addition to other subjective scales.

These self-reports, including the primary endpoint, are the accepted endpoints to evaluate the abuse potential of drugs. I'll now present the data from each study.

In the oral Category 3 study, we compared the abuse potential of intact and manipulated Ventrela to placebo and hydrocodone API as the control. This graph shows the bipolar drug-liking

results, where 50 indicates neither liking nor disliking and 100 indicates strong liking. As shown here, we see that mean liking scores for placebo and intact Ventrela remained at approximately 50, meaning no change in drug liking.

As expected, we see that mean scores rose quickly for hydrocodone API, demonstrating increased drug liking. These scores remained in the liking range of the scale between 45 minutes and approximately six hours after administration. Consistent with the PK profiles in the Category 2 studies, the pharmacodynamic profile of manipulated Ventrela showed a slower rise in drug-liking scores compared to hydrocodone API.

Peak drug liking was also lower with manipulated Ventrela. The oral study's primary endpoint of drug liking was also met. There was a statistically significant reduction in drug liking Emax for manipulated oral Ventrela compared to hydrocodone API.

Consistent with the time course graph, Emax for intact Ventrela ER was also significantly lower

than hydrocodone API and similar to placebo. In addition to the primary endpoint, highly relevant key secondary endpoints, such as overall drug liking, also showed significantly lower effects of manipulated and intact Ventrela compared to the hydrocodone API control.

When looking at the secondary endpoint of take drug again, we also showed significantly lower effects.

I will now show the results of the intranasal abuse potential study. In this study, we compared the abuse potential of intact and manipulated Ventrela to hydrocodone API, placebo, and manipulated Zohydro ER. Consistent with the oral study, placebo and intact Ventrela showed no clinically relevant change in drug liking.

In comparison, hydrocodone API, in red, and manipulated Zohydro, in yellow, demonstrated relatively rapid increases in drug liking, as might be expected from an immediate-release product. Again, we see lower drug liking for manipulated Ventrela.

When administered intranasally, Ventrela was associated with a slower rise in drug liking, with a lower peak effect, compared to hydrocodone API and manipulated Zohydro ER.

This slide shows the primary endpoint in the intranasal human abuse potential study with each test product. There was a statistically significant reduction in drug liking for manipulated intranasal Ventrela compared with both the hydrocodone API and manipulated Zohydro.

As in the oral study, the intact Ventrela drug liking was similar to placebo. The intranasal study had an additional primary endpoint of overall drug liking, which also met statistical significance, when Ventrela ER and manipulated Ventrela were compared to hydrocodone API and manipulated Zohydro ER.

In addition, another relevant endpoint of take drug again showed similar statistical significance when Ventrela ER intact and manipulated were compared to hydrocodone API.

This table summarizes the results of the

primary and key secondary endpoints. In addition to the statistically significant differences in the endpoints discussed thus far, we also saw statistical differences in the secondary endpoints of good effects and any effects.

The totality of Category 3 data support that Ventrela ER may have a meaningful impact on abuse in the real-world setting.

To summarize, the Category 3 pharmacodynamic results were consistent with the Category 2 pharmacokinetic results.

The human abuse potential studies demonstrated significantly lower drug liking for manipulated Ventrela compared with the non-abuse-deterrent comparators. It also showed consistent results across other relevant endpoints, including overall drug liking and willingness to take the drug again.

These data demonstrate that Ventrela shows abuse deterrence of manipulated tablets for the two most common routes of hydrocodone abuse.

Thank you. Dr. Malamut will now present the

summary and benefit-risk profile.

**Applicant Presentation - Richard Malamut**

DR. MALAMUT: Thank you, Dr. Webster. I'll briefly summarize our data and address our overall benefit-risk.

Clinical data has demonstrated significant pain relief compared to placebo in study 3103 and clinical data from our phase 3 studies demonstrate a safety profile typical of opioid products.

This data from our phase 3 program, when combined with previous findings for the reference drug, Vicoprofen, support efficacy and safety of Ventrela for patients with chronic pain. Our Category 1 in vitro studies demonstrated that Ventrela maintained its extended-release profile, even after applying techniques, methods, and practices known to be used for abuse.

Following the most likely methods of chemical and physical manipulation, Ventrela ER demonstrated physical and chemical properties expected to deter abuse via the oral, intranasal, and intravenous injection routes. These findings

suggest that Ventrela ER will be less attractive for abuse.

In Category 2 PK studies, Ventrela ER was shown to retain extended-release properties following manipulation. These studies demonstrated that when manipulated for oral or intranasal abuse, Ventrela exhibited a lower extent and rate of rise in hydrocodone concentration, lower Cmax, and later Tmax than non-abuse-deterrent opioids.

Finally, our Category 3 pharmacodynamic studies were consistent with the Category 2 pharmacokinetic studies. The human abuse potential studies demonstrated that manipulated Ventrela maintains its abuse-deterrent properties and resulted in reduced human abuse potential for the two most common routes of abuse, oral and intranasal.

It also showed consistent results across other relevant endpoints, including significantly lower overall drug liking and willingness to take the drug again. Importantly, abuse deterrence is expected to be confirmed in post-marketing, real-

world abuse Category 4 studies.

Teva is committed to responsible pain management, while protecting the overall public health. Our overall goal is to promote appropriate opioid use. We will maintain our high level of commitment to internal audits, training, and compliance.

Teva will also join the extended-release, long-acting opioid analgesic REMS program, and Teva will participate in the 11 shared FDA-mandated observational post-market requirement studies, as all Ventrela-specific PMR studies.

In summary, we believe that Ventrela ER has a positive benefit-risk profile for patients who suffer from chronic pain. Aligned with the FDA guidance, the goal of an abuse-deterrent opioid is to create an abuse deterrent and not an abuse-proof product.

Across the Category 1, 2, and 3 studies, Ventrela ER consistently demonstrated statistically significant and clinically meaningful reductions in risk for abuse when compared to non-abuse-deterrent

products.

Ventrela provides effective management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options have been inadequate.

Our data is consistent with the safety profile of existing extended-release opioid analgesics. We strongly believe that access to effective abuse-deterrent opioids for people with pain is needed, while still protecting the wider public health.

Ventrela ER will offer patients and healthcare providers an option to adequately and safely manage chronic pain, while at the same time providing part of the solution to the current public health issue of prescription opioid abuse.

Thank you. We're now pleased to take your questions.

**Clarifying Questions**

DR. BROWN: Thank you for your presentation. Are there any clarifying questions for Teva? Please remember to state your name for the record

before you speak.

If you can, please direct questions to a specific presenter.

Dr. Emala?

DR. EMALA: Hi, Charles Emala. I have a question for Dr. Webster and then Dr. Moe. Dr. Webster, in the Category 3 studies, the term "manipulation" is used a lot. Could you clarify what the manipulation was?

DR. MALAMUT: Dr. Webster, can you discuss the manipulation of our products? Actually, before Dr. Webster, let me have Mary Bond address that question first, if I may.

MS. BOND: Good morning. Mary Bond, clinical pharmacology at Teva. For our Category 3 studies, in the oral study, we utilized Tool F and in the intranasal study, we utilized Tool C.

DR. EMALA: So that was without any kind of extraction.

MS. BOND: Correct.

DR. EMALA: Thank you. That leads to my follow-up question for Dr. Moe related to slide 45

in the presentation. I'm trying to reconcile the data in this slide with the data presented in the briefing document.

This slide shows Tool A in Solvent H at 30 minutes released 10 percent. Is it possible to pull up the briefing document, Figure 6, from the sponsor?

That 10 percent at 30 minutes is shown in Figure 6 to go to 62 percent. I'm trying to reconcile the difference. I assume because agitation was included in the figure in the briefing document. And then that 62 percent goes to 89 percent extraction at two hours in Solvent H.

My question is Solvent H, which appears to be widely available to a potential abuser, as does the temperature and tool used in this method, I'm curious about the volume used here and whether it was considered whether drying this extraction could then present the drug in a way that could be altered for not only oral, but other routes of abuse.

DR. MALAMUT: Dr. Moe, may I put you to the

microphone to address those questions, please?

DR. MOE: Actually, the purpose of the experiments shown here in this and the other slide are -- really, for somebody who first manipulates the product, they dissolve it up for subsequent ingestion of that solution. The types of tests that you're referring to, where you then isolate that solid from that solution, is actually the next type of study, what we call the advanced solvent.

DR. EMALA: I'm sorry. I asked a long question. But the first step here would be putting it in Solvent H with agitation for 30 minutes to two hours.

DR. MOE: Correct.

DR. EMALA: Potential oral ingestion. And my follow-up question to that was would it subsequently be possible to then dry it for alternative modes of use.

DR. MOE: Right. Certainly, somebody could do that. But, again, when we were trying to do that mechanism, the chemical extraction studies go after that, but yes, somebody could also do that,

yes, with these solutions.

DR. EMALA: Do we know the volume that that study was done in? Is it even practical to think about drying that solvent? If it's a large volume, I would think it would be impractical to try to dry it.

DR. MOE: I'm not sure I can talk volumes in the open session.

DR. EMALA: Thank you.

DR. HERTZ: This is Sharon Hertz. You can comment in general in terms of it being a large or small volume.

DR. MOE: Well, it's not on the order of a bathtub, but it would certainly be a time-consuming process to dry it off.

DR. BROWN: Dr. Choudhry?

DR. CHOUDHRY: This question is for Dr. Webster, at slide 60. I'm just curious about the choice of comparison between the oral studies and the intranasal studies. Here, we have data comparing Ventrela to hydrocodone, whereas in the intranasal studies, we also add in then the

comparison to Zohydro.

I'm just curious if you can comment a little bit on the choice of comparison here and why, in the oral study, the Zohydro was not included.

DR. MALAMUT: Yes. Quite simply, Zohydro did come to market just prior to initiating the nasal human abuse potential study, so we did include it in that study. Hysingla was not available at the time of these studies.

DR. BROWN: Dr. Morrato?

DR. MORRATO: Yes. This is Elaine Morrato. I had two questions, I think one for Dr. Moe and the other one for Dr. Webster. So the one for Dr. Moe, I'm trying to better understand the chemical mechanism of action as the basis for the abuse deterrent.

I do understand, from what you've mentioned in the briefing document, that it's not intended to be physically difficult to manipulate.

You quote that, "The rational selection of excipients in manufacturing process steps are what's the barrier," I was hoping that you could

elaborate a little bit more to help us understand the scientific basis.

DR. MALAMUT: Dr. Moe, may I invite you to the microphone?

DR. MOE: I'm going to talk generally so, hopefully, we can get to a full understanding here. We mentioned in the presentation that there's three layers. So what we start with is the drug itself, the hydrocodone, and it's combined, first, with two different polymers.

It's important that they are different polymers at the very inner part of these, because they're different solubilities. And the concept there is they're radically different, so one is going to be more soluble in ethanol, one is going to be more soluble in water.

That way, it's going to pose a problem no matter what type of that kind of solvent. One of them is going to gel and then make it, because they're very highly viscous.

Then, beyond that, we take those particles and we coat them with a barrier, and that barrier

is actually a very strong barrier. But it's interesting, because the inner granules are actually pliable. They're, I'll just say, squishy. And then you have a nice, hard coating around that.

Both of these impart some measures of extended release, but they're all high viscosity. When you start extracting the layers down, it's going to be hard to get to that raw API.

Then, on top of that, now we take thousands of these little particles and we incorporate that into the tablet matrix.

The tablet matrix itself adds some more high-viscosity polymers, and so that's especially important when you grind it up and try to extract it into small volumes for IV or something like that. It's now everything, all the way down.

When an abuser is going to try to crush this, he may get the illusion of I have crushed it, I have beaten it, and yet you have these very hard particles in there that can survive that, still maintain an extended-release profile, and show an improvement over a non-abuse-deterrent, as we have

shown across the range of the Category 1 studies.

DR. MORRATO: Thank you. The core, then, when you have the three particles at the core, are they agglomerated or are they just sort of --

DR. MOE: Yes. So the schematic we had shown earlier was simply that. It is a schematic. Certainly, they all start like that. They're not perfectly spherical like that. But you have the drug itself, which is a micronized drug, very small. You have the polymers. One of them is actually sprayed on as a solution and the other one based on the solvent combination that we use. It's not a pure solvent either one way or the other.

The whole thing ends up being more like a very small piece of chewing gum. It's all intertwined. It's certainly not going to look like that. It's going to look like just a gooey mess.

Does that work?

(Laughter.)

DR. MORRATO: Yes. In other words, the picture that we saw made it look like if I were to take an over-the-counter product and break up the

capsule and I get all these little pieces or if I go to get my Dippin' Dots and I have all the little dots of ice cream and they're all just -- that's the picture we saw.

DR. MOE: Yes.

DR. MORRATO: What you're saying is that they're more chemically intertwined with one another. It's not like you can easily separate at the core..

DR. MALAMUT: Yes. They really are. They're, I can't say molecularly dispersed, because that's not quite fair, but again, the drug itself does start out at the micron size. At the micron size, they're all very much intertwined and they're also a little bit irregular, too. When the next coating goes over that, it fills in the gaps and you end up with a spherical particle at the end, but everything inside there is all pretty complicated.

DR. MORRATO: Thank you for clarifying. My other question was for Dr. Webster and it has to do with the Category 3 studies. And I'm just

wondering if you might comment on -- I mean, it makes a very nice story where the intact tablet is worse than placebo in terms of abuse deterrent, manipulated somewhere between that, and the controls, and so forth.

But I also recognize that this is a qualified selected user group that was in these studies. So saying that it's equivalent to placebo makes me wonder, all right, what's going on there, because we know in the efficacy studies, it's working.

Is it really abuse deterrent in the broad sense, I guess, or is it really abuse deterrent among those that are already recreationally using the product?

I'd like to hear your thoughts on how we best interpret the generalizability of that information.

DR. MOE: I'd like Dr. Webster to come to the microphone just to talk about our patient population and a bit about the generalizability of these studies.

DR. WEBSTER: So if I understand your question correctly, you are trying to understand why, when it's not manipulated, it's like a placebo, but when it's -- and the population, how that fits with the population.

First, the population is screened. It's basically an enriched population. They have to be given hydrocodone and they have to demonstrate a significant liking. They have to have a 15-millimeter positive response above placebo. So if there's a 5 placebo, you have to have 20, and that's a fair distance already on that scale of 50 to 100.

But they are non-dependent and they are given naloxone, as you know. They have not increased tolerance. They're going to be sensitive, but they're of the type of people who like the effect, so they're sensitive.

This population may be the type of people that need a little bit more drug in order to push it up, but that would be genetically based, not because of exposure, because just taking it

irregularly, which is what they have to do to be able to not be dependent when they come in, does represent the people who use it.

That's the whole purpose. For many of us who don't use it, we may get nauseated from an opioid and that's why we don't use it. It's the negative effects. But those who like it, this is, I think, very typical of the response of those who like these drugs and want to abuse it, how they would respond.

DR. MORRATO: The deterrence is among those that are liking and wanting to abuse as opposed to --

DR. WEBSTER: I'm sorry. I can't hear you.

DR. MORRATO: Yes. When we say abuse deterrent orally, we're really saying orally among a subset of people who are already using it.

DR. WEBSTER: Well, I think it's deterrent. We don't measure all of the normal population who don't like opioids, because they don't need the deterrent. They're not going to take it. What we want to do is prevent --

DR. MORRATO: But I'm talking about patients who are taking it chronically. I understand it's a spectrum.

DR. WEBSTER: Right.

DR. MORRATO: Maybe you might have other information. What proportion of patients, then, are routinely being screened that then get selected for this study? How hard is it to find these kinds of study subjects once they've identified as a recreational user?

DR. WEBSTER: It varies a little bit, depending on the molecule that we're looking at and what the thresholds are. There are a lot of variables. But generally, about 50 percent of the people that screen get enrolled into the study. You'll have 30 percent or so, maybe even 50 percent depending, of those fail screening and then they'll fail the discrimination phase, and then they're enrolled. Fair enough?

DR. MORRATO: Yes. Thank you very much for clarifying.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: Brian Bateman. This question is for Dr. Malamut and relates to slide 46. I'm wondering if you can review for us the results from the aqueous extraction studies that were done with the combinations of stressors that yielded greater than 80 percent release.

I think it would be useful to have a sense of how complex these extraction methods are. And I understand they don't need to be in the coated form, but is it a combination of temperature, agitation, and particular solvents?

DR. MALAMUT: Dr. Moe, can you clarify our procedure used for our extraction techniques?

DR. MOE: Here are the specific conditions up on the screen. Again, this is first manipulated. And as we showed with the oral ingestion, when you take specifically the powder, you can't defeat it. And then we started different extractions.

As you ramp them up, these are, again, the set of conditions that do achieve greater than 80 percent of drug release following manipulation at a

half-hour outside the body.

DR. BROWN: Dr. Walsh?

DR. WALSH: Thank you. Sharon Walsh. I have several questions, probably all which should be directed to Dr. Webster, related to the abuse potential studies. My first one is just to follow up on Dr. Morrato's question. I'm wondering what the qualification dose was used in the qualification phase.

My second question is that I'm somewhat surprised by the absence of any measure of error for all the time-action figures for the dynamic and the kinetic data, and I'm wondering whether or not we can see the dynamic outcomes with some standard error of the mean shown on the figures to give us some idea of the individual variability in response.

Then my final question goes back to the subject characteristics in the study, and I'm just wondering if you can tell us, for the oral and intranasal Category 3 studies, more about the recent opioid use history with respect to frequency

and route for the people that were enrolled and whether or not their use was verified objectively with urinalysis.

DR. MALAMUT: Mary Bond, can you address part of those questions, our qualification dose and characteristics of the enrolled?

MS. BOND: Sure. The qualification dose in each of the Category 3 studies was the same dose that was administered in the treatment phase, and that was a dose of 45 milligrams.

Can you repeat the part of the question about the actual population and verifying their usage, et cetera?

DR. WALSH: Yes. In the briefing document, the participants were described as recreational drug abusers and it didn't really specify any details about their actual opioid use histories, which I think is relevant here. So if you have detailed information on frequency of use, route.

MS. BOND: Yes. What we would require per our inclusion/exclusion criteria is that these individuals have a history of use at least 10 times

in their lifetime, at least once in the past 12 weeks, that they have a preference for opioids, and that they use via the route under study.

DR. MALAMUT: Then just to clarify your question on additional statistical analyses, it was for Category 3 studies.

DR. WALSH: Yes, for Category 3. I think it's more important for the Category 3 and it's not really about the analysis. It's about the presentation of the data, that none of the time-action curves show any measure of individual variability or the group variability. And I'm wondering whether or not you have those figures with the means and the standard errors represented.

DR. MALAMUT: Yes. I'd like to invite Dr. Bond, Mary Bond. Can you come to the microphone and address that question, please?

MS. BOND: We do have figures, also, with error bars provided that are available for you to view, we do have for our oral study. And then we would also have a similar representation for our intranasal study.

DR. BROWN: Can we see the intranasal study, especially related to slide number 64? Could you put that back up?

DR. MALAMUT: I'm sorry. What was that? I couldn't hear you.

DR. WALSH: I think he'd like to see the one with the error bars back up for the intranasal study. I just want to clarify. Can you tell me, are we looking at standard error of the mean? Now, this is standard deviation. Okay.

DR. BROWN: Comments or questions about that? Dr. Morrato?

DR. MORRATO: When you are saying that one is better than the other, is that one based on a qualitative assessment of the means or is it based statistically? Can you remind us?

DR. MALAMUT: Yes. It's on means.

DR. MORRATO: Are there any that achieve statistical significance in the studies?

DR. MALAMUT: Mary Bond, would you mind addressing that?

MS. BOND: The conclusions are based upon a

statistical assessment of peak drug liking. So it does look at the Emax of that at-the-moment drug-liking score and the difference between treatments.

DR. WALSH: Could I just follow up on that? Did you do a statistical analysis of the time-action curves across conditions to compare them to one another? Also, did you do a comparison of the full area under the curve, exposures with the statistical analysis? I saw the Emax analysis in here. The data that we're looking at right now on this slide for the full time course, how were those data analyzed?

It's important, because those are actually the raw data.

DR. MALAMUT: Mary Bond, can you address that question, please?

MS. BOND: Just to be sure that I'm understanding your question, are you asking if we did a statistical comparison of the AUEC, the area under the effect curves, for drug liking?

DR. WALSH: I was actually asking for either time course analysis, time by condition, and the

full area under the curve analysis by condition.

I guess I just want to say one more thing, that looking at those outcomes for the pharmacodynamics with the error measures makes me also want to look at the PK outcomes with the error measures, if we can do that.

MS. BOND: As far as a time course analysis, that was not performed. We did look at area under the effect curve analyses. I'm not sure if we have those data in a back-up slide that I may be able to pull up to show you the results of those. We're looking for AUEC compared to one another by treatment.

We may need to provide some information regarding that after the break for you.

DR. WALSH: That would be fine. Can you define that? What is the AUC for the effect? How far out does that go in your time curves?

MS. BOND: Yes. We measured the liking measures and all of the endpoints, really, over 24 hours post-dose. We do have it for 24 hours.

DR. WALSH: The area under the curve that

we'll see is for 24 hours.

MS. BOND: Yes. That's correct.

DR. WALSH: Thank you. And just the PK slides, if possible, with the errors.

MS. BOND: We do have those, as well.

DR. BROWN: Dr. Sprintz?

DR. SPRINTZ: Yes. I guess my first question was initially --

DR. MALAMUT: Let's put that back up.

MS. BOND: As requested, these are the time course curves per treatment for the intranasal study, with error bars for standard deviation. And we have the same, also, for the oral study, if you would like me to put that up or hold a moment.

DR. BROWN: Dr. Sprintz?

DR. SPRINTZ: Thanks. My first question, which may have been answered earlier, was, initially, why did you not compare any of these studies against the abuse-deterrent formulations of the Zohydro ER. And I think you were saying it wasn't available.

DR. MALAMUT: Yes. Again, when we conducted

the phase 3 studies you're referring to, Zohydro ER was not available.

In fact, the only study that Zohydro ER was available for was our intranasal human abuse potential study.

DR. HERTZ: Just as a minor correction, we don't recognize any of the Zohydro as having any abuse-deterrent properties. We are aware that there are different formulations, but none of them have demonstrated abuse-deterrent properties that are suitable for labeling, so we don't consider Zohydro to be abuse deterrent.

There are six products currently abuse deterrent that have labeling consistent with our guidance. That's not one of them.

DR. SPRINTZ: Thank you. And then the other abuse-deterrent formulation, which, I'm assuming, of hydrocodone was not available at the time.

DR. MALAMUT: Hysingla, yes. It was not available at the time of any of these studies.

DR. SPRINTZ: Thank you. I have one other question for, I guess, Dr. Webster. In the patient

selections that you had, were they pain patients or or non-pain patients?

DR. MALAMUT: Dr. Webster, can you address that question, please?

DR. WEBSTER: They're not pain patients. These are individuals that are just mostly college students. These are healthy individuals who are recreational drug users.

DR. SPRINTZ: Then the other question was how did you monitor those patients to make sure they weren't taking other meds, like benzos, carisoprodol, or illicits?

DR. WEBSTER: Prior to being admitted or during the testing?

DR. SPRINTZ: Both.

DR. WEBSTER: Regardless, it's always urine drug testing. We do urine drug testing.

DR. SPRINTZ: You did do that throughout this study.

DR. WEBSTER: Yes, yes. That's part of screening. That's part of before screening and entry. And if, in a study like this, they're

discharged, then when they come back in, they have to be screened, as well.

DR. SPRINTZ: I got you. Thank you.

DR. BROWN: We're going to take a break now. We're going to defer -- there are some other folks that have questions and we're going to defer those until this afternoon. Everybody is going to get their opportunity to put questions to the Teva group.

This will be a 15-minute break. Please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. And we're going to resume at 11:20.

(Whereupon, at 11:05 a.m., a recess was taken.)

DR. BROWN: We're now going to proceed with the FDA presentations.

**FDA Presentation - Joann Lee**

DR. LEE: Good morning. I'm Joann Lee, drug utilization analyst in the Division of Epidemiology within the Office of Surveillance and Epidemiology.

For the next few minutes, I'd like to briefly present drug utilization patterns of hydrocodone extended-release and other extended-release or long-acting opioid analgesics from 2011 through 2015.

I shall provide context for the discussions taking place today. First, I'll discuss the sales distribution of extended-release opioid products, followed by prescription utilization of hydrocodone extended-release and other extended-release or opioid analgesics, focusing on the outpatient retail pharmacy settings.

I'll then present our findings on top prescriber specialties of hydrocodone extended-release, and finish with limitations and summary.

For this presentation, we'll focus on hydrocodone extended-release, because today's discussion involves another hydrocodone extended-release product or Ventrela ER. We also looked at other extended-release or long-acting opioid products, as shown on this slide, which is the opioid market into which Ventrela ER will be

introduced, if this drug is approved.

This opioid market includes methadone, morphine, oxycodone, hydromorphone, oxymorphone, and tapentadol, along with transdermal patches, fentanyl and buprenorphine.

To determine the primary settings of care, we used the IMS National Sales Perspectives database to provide the sales distribution data of hydrocodone extended-release products that were sold from manufacturers and wholesalers into the various settings of care.

Please do note these sales data are nationally projected to all settings of care.

As displayed in this chart, 94 percent of hydrocodone extended-release products were distributed from manufacturers to retail settings. Additionally, a majority of each of the other extended-release or long-acting opioid products that I described earlier and included in this review were also distributed to the retail settings.

Based on these sales data, we focused on the

U.S. outpatient retail pharmacies.

For the prescription data analysis that I'll present next, we used the IMS Health National Prescription database. This measures the dispensing of prescriptions from retail pharmacies into the hands of consumers through prescriptions within the United States. These prescription data can be stratified by prescriber specialty.

Now, to present our findings, this figure shows the national estimated number of prescriptions dispensed for the extended-release or long-acting opioid analgesics through the U.S. outpatient retail pharmacies from 2011 through 2015.

Let me draw your attention to the bottom of this graph. As shown here, hydrocodone extended-release products were initially marketed in the United States starting in 2014. Therefore, prescription data for these products are shown here for the two-year [sic] time period from 2014 to 2015.

Since marketing of these hydrocodone

extended-release products, namely, Zohydro and Hysingla, the uptake in prescriptions dispensed was approximately 150,000 prescriptions in 2015. This accounts for less than 1 percent of the prescriptions dispensed for the extended-release long-acting opioid analgesics market.

This chart shows the top prescribing specialties for hydrocodone extended-release in 2015. Approximately 21 percent of hydrocodone extended-release prescriptions were written by family practice, general practice, and osteopathy, followed by anesthesiology at 18 percent of the prescriptions written and so on.

Also, pain medicine accounted for 10 percent of the prescriptions written for hydrocodone extended-release analgesic products. A couple limitations to consider are that only outpatient retail pharmacy was assessed. That is, inpatient and mail-order data were not included in this analysis. And the top specialties that prescribe hydrocodone extended-release were captured as reported by the prescription data.

To summarize, this is marketing of hydrocodone extended-release products Zohydro and Hysingla that began in 2014, the uptake in prescriptions dispensed was approximately 150,000 prescriptions in 2015, accounting for less than 1 percent of the prescriptions dispensed for the extended-release or long-acting opioid analgesics market.

The top prescriber specialties, again, were family practice, general practice, osteopathy, followed by anesthesiology for the hydrocodone extended-release products.

With that, Dr. Levin will present next. Thank you for your attention.

**FDA Presentation - Robert Levin**

DR. LEVIN: Good morning. My name is Dr. Robert Levin. I am a medical officer in the Division of Anesthesia, Analgesia, and Addiction Products. This morning, I will be talking about the following topics related to the proposed abuse-deterrent labeling, an overview of Section 9.2 Drug Abuse; class language on drug abuse; risks specific

to abuse of Ventrela ER; abuse deterrence studies, including in vitro testing and clinical human abuse potential studies; the abuse potential endpoints of drug liking and take drug again; oral and intranasal abuse potential studies; and, a summary of the product's abuse-deterrent properties.

The extended-release long-acting opioids as a class contain the following language about abuse potential. This same language will be included in the proposed label for Ventrela ER. Ventrela ER contains hydrocodone, a substance with a high potential for abuse, similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone.

Ventrela ER can be abused and is subject to misuse, abuse, addiction, and criminal diversion. The high drug content in the extended-release formulation adds to the risk of adverse outcomes from abuse and misuse.

All patients treated with opioids require careful monitoring for signs of abuse and addiction.

In addition, the following information in

the label is more specific to Ventrela ER. Ventrela ER is for oral use only. Abuse of Ventrela ER poses a risk of overdose and death.

The risk is increased with concurrent use of alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved Ventrela ER enhances drug release and increases the risk of overdose and death.

You have heard about the in vitro laboratory studies that were done to explore the different methods that might be employed to defeat the extended-release and the abuse-deterrent properties of Ventrela ER. The following statements in the label will summarize the results of those in-vitro studies.

Physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation of Ventrela ER.

Results support that Ventrela ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-

release properties despite manipulation. When Ventrela ER was subjected to attempts at small volume extraction, the resulting material was viscous and resisted passage through a hypodermic needle.

You have also heard about the two human abuse liability studies that were performed with Ventrela ER. The first explored the potential for oral abuse, and the second explored the potential for intranasal abuse. The results for the following two endpoints will be summarized in the labeling for both studies.

Take drug again was measured on a bipolar 100-point visual analog scale, where 0 represents strongest negative response, definitely would not take the drug again, 50 represents a neutral response, and 100 represents the strongest positive response, definitely would take the drug again.

Drug liking was measured on a bipolar 100-point visual analog scale, where 0 represents maximum disliking, 50 represents a neutral response, and 100 represents maximum liking.

The next three slides summarize the proposed labeling to describe the oral abuse potential study. As you heard, the study was a randomized, double-blind placebo- and active-controlled, four-period, crossover study in non-dependent opioid abusers. Thirty-five of the 49 enrolled subjects completed all treatment conditions, 45 milligrams of Ventrela ER intact, 45 milligrams of Ventrela ER finely crushed, 45 milligrams of hydrocodone bitartrate powder, immediate release, and placebo.

The oral administration of finely crushed Ventrela ER was associated with statistically significantly lower mean scores for drug liking and take drug again, p less than 0.001 for both, compared with powdered hydrocodone, as summarized in the following table.

This table will be included in the label and summarizes the results for four treatment groups. Note that the mean take drug again score for the finely crushed Ventrela ER is 55.9, which you can see in the second row from the bottom, and is less than the immediate-release hydrocodone powder,

75.1.

A similar pattern is seen for the means of drug liking. This figure will be included in the label to summarize the percent reduction in drug liking for finely crushed Ventrela ER compared to the immediate-release hydrocodone powder. The Y-axis represents the percent of subjects attaining a percent reduction greater than or equal to the value on the X-axis.

For example, about 80 percent of subjects experienced some reduction in drug liking with Ventrela ER compared to immediate-release hydrocodone, and about 20 percent experienced no reduction. For about 70 percent, the reduction was 30 percent or more; and, for about 60 percent, the reduction was 50 percent or more.

The next three slides summarize the proposed labeling to describe the intranasal abuse potential study. As you heard, the study was a randomized, double-blind, placebo- and active-controlled study in non-dependent opioid abusers. Thirty-four of the 45 subjects enrolled completed all treatment

conditions. Intranasal administration of 45 milligrams Ventrela ER finely milled, 45 milligrams of hydrocodone bitartrate powder immediate release, oral administration of 45 milligrams Ventrela ER intact, and intranasal administration of placebo.

The intranasal administration of finely milled Ventrela ER was associated with statistically significantly lower mean and median scores for drug liking and take drug again. P less than 0.001 for both compared with powdered hydrocodone, as summarized in the following table.

This table will be included in the label and summarizes the results for three intranasal treatment groups. Note that the mean take drug again score for the finely crushed Ventrela ER is 67.5, which you can see under the Ventrela ER column, the last column in the table, and is less than the immediate-release hydrocodone powder, 75.5. A similar pattern is seen for the means of drug liking.

This figure will be included in the label to summarize the percent reduction in drug liking for

finely milled Ventrela ER compared to the immediate-release hydrocodone powder.

The Y-axis represents the percent of subjects attaining a percent reduction greater than or equal to the value on the X-axis. For example, about 75 percent of subjects experienced some reduction in drug liking with Ventrela ER compared to immediate-release hydrocodone, and 25 percent experienced no change.

For 35 percent, the reduction was 30 percent or more; and, for about 20 percent, the reduction was 50 percent or more.

This summary of the abuse-deterrent properties of Ventrela ER will appear at the end of Section 9.2 of the label.

The in vitro data demonstrate that Ventrela ER has physical and chemical properties that are expected to deter intravenous abuse. The data from the in vitro studies and clinical studies indicate that Ventrela ER has physiochemical properties that are expected to reduce abuse via the oral route and via the intranasal route. However, abuse of

Ventrela ER by the intravenous, nasal, and oral routes is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of Ventrela ER on the abuse liability of the drug.

This concludes my presentation.

**Clarifying Questions**

DR. BROWN: Thank you, Dr. Levin.

Are there any clarifying questions for the FDA? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. Dr. Choudhry?

DR. CHOUDHRY: Thanks. Niteesh Choudhry. I have two quick questions for Dr. Lee and one for Dr. Levin. Dr. Lee, I just wanted to confirm that the IMS prescription audit data, since it comes from retail pharmacies, does include cash prescriptions, cash-paid prescriptions. That's number one.

Number two, for Dr. Lee, I'm wondering if you're aware of trends in utilization of other

abuse-deterrent products when they've come to market. Do you have anything to speak about, using IMS or other data? That's my question to you.

Dr. Levin, just to get it on the record and you can comment, I'm just wondering. This follows-up on something Dr. Walsh was getting at before, this idea of what the right outcome is for a lot of those studies, when we look at drug liking and we're seeing statistics here and proposed labeling around the Emax.

I'm just wondering if you could comment a little bit about Emax versus area under the curve versus some sort of other temporal trend relationships.

Those are my three questions.

DR. LEE: For your first question, that is correct. It included cash transactions. And for your second question, we did not look into the abuse-deterrent products. But because they're newly approved, it should be fairly low. Does that help?

DR. HERTZ: I'm going to respond to your

second part. Our approach to understanding or thinking about abuse-deterrent products and the studies has been growing over time as we've been gaining experience in trying to sort through all this.

We used studies that were previously used predominantly for scheduling and establishing abuse liability in a more basic sense, and we found that study design useful as we decided how to try and evaluate abuse-deterrent properties.

The division has worked closely with the controlled substances staff, for instance, and we had some earlier advisory committee meetings where we discussed these evaluations, as well. I think they go back to 2008 or 2009 when this was all even newer.

What we have evolved and that's represented in the guidance -- and I think we might have even gone a little further in our thinking, even though it's a fairly recent guidance, is when we think about the outcomes that are commonly used, the pharmacodynamic outcomes in the Category 3 studies,

we have drug liking, drug high, and take drug again as the big three.

When we're dealing with a drug that's going to be Schedule II, it's got abuse liability. Right? When we say that, in general, abuse deterrent is not the same as abuse proof, it's because it has to deliver the opioid, so it's going to have the abuse potential.

What are the characteristics of the product that would suggest the likelihood of a deterrent effect by one or more routes, and how do we evaluate that? If the drug is less liked or produces less high, that's probably good. But is it good enough?

Then you get to the discussion of what's the clinically relevant amount of difference, because as we know, even from the efficacy and safety side, sometimes a statistically significant difference in an outcome measure doesn't necessarily mean it's a clinically relevant difference for a variety of reasons.

I think most of the folks on the committee

don't necessarily need me to go into that concept. But it's the same thing for these outcomes. We looked very hard at take drug again, because it seems that if someone is less likely to take drug again, it provides additional relevance. You're asking someone, do you want to take it again. If they actually want to take it less than the comparator and they either like it less or it creates less high, or in some settings perhaps with aversive technology, it causes enough adverse effects that, in spite of similar high or liking, they still don't want to take it as much, then perhaps that's a way to give the findings or the product some kind of clinical relevance to the other outcomes.

That's why we focus on the take drug again piece more so perhaps than would be the case in an actual study to assess whether, for instance, a new molecular entity, what kind of abuse liability it has.

Then in terms of whether we should use the AUC or the Emax, a lot of the work that's been

done -- and I think that, perhaps, there's folks on the committee who might be able to speak to this even better, but it seems that -- and we've heard over time about this, as well -- there are certain characteristics of the profile, PK, but, also, the PD profile that are attractive for the purposes of abuse.

It is about the maximum effect and how quickly that occurs. We look at Emax, because if the only difference is it takes longer, but everything else is the same, I think we feel that a motivated abuser would potentially plan ahead and maybe take the drug a little earlier if they want to have an effect at a certain time in the evening or what have you. So, yes, some of it is based on assumptions.

But I think some of the assumptions we try to tie into what's known about the behavior in the context of intentional abuse of the opioid. We do rely on Emax and we do heavily weigh the take drug again to help us understand the clinical relevance of the other parameters.

DR. BROWN: Dr. Gerhard?

DR. GERHARD: Toby Gerhard, Rutgers. This is a question for FDA. I'm not quite sure for whom at FDA. I would just be interested to put the discussion regarding the abuse-deterrent formulations in general in the context of the opiate epidemic we heard about in the introduction of this meeting.

To, obviously, only a proportion -- and I'm not sure about the size of the proportion -- of the issues that we have with opiates in the country are amenable to being addressed with abuse-deterrent formulations.

The intentional abuse is something that can be addressed, but questions of addiction and other types of misuse that aren't intentional abuse are not.

Do we have any data regarding the magnitude of the abuse issue within the larger context of the opiate epidemic? And just as a quick follow-up, I think the context, while it's certainly very useful and important to have abuse-deterrent formulations,

the impression, obviously, that I think is extremely important to avoid is that these formulations would be, in a sense, safe opiates that could be used without the concerns that we generally would have in situations where that doesn't apply at all.

Certain people, certain addiction issues, and other misuse issues are just not addressed by abuse-deterrent formulations.

I think that's the context of the question, in my mind.

DR. HERTZ: I really want to answer that, but I'm not going to, for two reasons. One is that right now, I want us to focus on clarifying questions. But, almost more importantly, I think that's a question for the committee to discuss. We have public statements about the role of abuse deterrent, trying to promote abuse-deterrent formulations as one element in, hopefully, the programs of what we're trying to do.

I think there are a lot of layers in your question and I think that is something we should

discuss in the context of some of the questions this afternoon.

In terms of how much FDA weights abuse deterrence over what I'll say is one element and we don't believe that it's a fix-all one-size solution, because we recognize that a Schedule II drug will always behave like a Schedule II drug and full mu opioid agonist will always have the properties of a full mu opioid agonist.

The reasons why these aren't abuse-proof formulations is because, as you can see, they are meant to change the profile so that they're less appealing for certain aspects. But it is a limited ability to address the total issue that we're facing in the country.

DR. GERHARD: Point well taken. But, still, is there any quantitative data that FDA has that relates to how much abuse there actually is in just the utilization numbers, like what proportion of opioids are abused versus misused or used according to the label? Do we have any idea?

DR. HERTZ: We have a number of different

data sources and I can't get into it now. I don't have it available. It has been presented in the past. We did go over some of it recently, in May, at the REMS advisory committee and, in particular, we went into some of the challenges of answering your question with specifics during the May 3rd and 4th advisory committee that we held. That was part of our REMS, the extended-release and long-acting opioid REMS review.

Again, I can't give you what you want. You're asking really god questions, but I think there's a lot of good information there.

DR. STAFFA: This is Judy Staffa. I'll add to that. I think the answer to your question is that we don't yet know. We don't know what percentage of the abuse problem as a whole is actually related to specific products or to specific formulations of specific products, and a lot of that has to do with the absence of good data on that. But I do think, if you go back to Dr. Lee's slides, the percentage, what we can know is the uptake of abuse-deterrent products.

As Dr. Hertz mentioned, there are six products that have been approved with abuse-deterrent labeling and the uptake has been small. If you look at that 150,000 prescriptions in the first year or in 2015, that's divided between two separate products, one of which has abuse-deterrent labeling, which is Hysingla, and the other does not.

That's comparable throughout the other six. It doesn't matter. They're just not uptaking quite a bit. And I know we've heard in other public meetings about the cost and other aspects. And again, at this point in time, we don't have data on any of these products about how well they perform in the real world and how well they deter the abuse we expect them to deter. But that work is underway.

I would say, to caveat, the only product that actually does have appreciable use in this space is the reformulated OxyContin, and you saw that in the graph. That's the lion's share of this class, actually.

DR. HERTZ: One last point is when we have more specific product data coming in, we will come back to you.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: This question is for Dr. Levin and it pertains to slide 13. The summary here suggests that FDA's perspective is that the in vitro studies indicate that the drug has properties that are expected to reduce abuse via the oral route.

But in the briefing document that we received from FDA, on page 52, the memorandum states, "The in vitro data submitted by the sponsor is not sufficient to establish any significant abuse deterrence by the oral route or its superiority over the comparator extended-release, single-entity hydrocodone product."

I was just hoping that Dr. Levin could reconcile those statements and give us a little bit of a sense of what FDA's thinking is on the in vitro studies.

DR. LEVIN: If you're referring to the

second bullet, I think that it's a combined of the in vitro and clinical studies together that led us to that conclusion.

DR. HERTZ: We don't have a final label yet. So it's still evolving. We tried, for a variety of reasons, not -- there's no fault here. There's not a problem that's underlying this, but just for a variety of reasons, we don't have what we would recommend or what we've agreed to as the final language.

This is the kind of labeling we are considering along with the company and you can weigh in if you feel that -- and we'll discuss this later. We want to hear what you think is the right way to convey information. If this is somehow unclear or misleading, let us know. We have opportunity. There's no final action.

DR. BATEMAN: We should interpret this as the proposed label and this memo as one reviewer's perspective on the data that were submitted.

DR. HERTZ: Yes.

DR. BATEMAN: Okay.

DR. BROWN: Dr. Hertz, do you have any comment on the information that we were provided prior to coming to the meeting and the fact that the statement was made that it didn't meet the criteria for abuse deterrence?

DR. HERTZ: I'm sorry. I didn't quite follow the question.

DR. BROWN: As Dr. Bateman said, the statement was made in the prep documents that the drug did not meet abuse deterrence criteria and the labeling appears to be 180 degrees from that. I'm just wondering if I'm missing something.

DR. HERTZ: I'd have to go back. The specific statement about the in vitro not supporting it, for oral, I think we agree, but I think what we were trying to convey in the language that was shown was that the clinical studies are supportive potentially of a claim or for labeling, if you agree.

But I think that more important than what our conclusions might have been is what your conclusions will be, because it's okay to disagree

with us. Clearly, I don't need to tell this committee that. You folks are quite comfortable disagreeing with us and that's good when we have a difference of opinion.

I'll go back and double-check exactly what that language is, but what Dr. Levin presented as a possible labeling of the outcomes is one option, but more importantly is ultimately what the committee thinks the studies support and then if there are suggestions for, with that in mind, what we should convey, that's really, I think, what's important.

DR. BROWN: Dr. Wesselmann?

DR. WESSELMANN: Ursula Wesselmann, University of Alabama at Birmingham. I was surprised that the data presented to us regarding drug liking, if they would take the drug again, were presented not differentiated between females and males. Is there any reason for that? Because the side effect profile can be different in males and females.

I was wondering if one group actually had

little difference to the drug as it will be formulated.

DR. HERTZ: I'm looking past to the sponsor to see if they have any of these analyses available by sex. I don't know if we do, but we'll double-check, as well.

DR. MALAMUT: Hi. Richard Malamut. Just to be clear, in the Category 3 studies you're referring to, the human abuse potential studies, do we have that data? We don't have that data by gender.

DR. HERTZ: I'll check our reviews, as well, and see if we can find that.

DR. BROWN: Dr. Perrone?

DR. PERRONE: Jeanmarie Perrone. First of all, I think that the data that we're seeing with Zohydro as a comparator, to me, reflects on our decision made three or four years ago voting against Zohydro and our concerns about it as having tremendous abuse potential as a drug coming out for the first time without acetaminophen in it and high dose and our concern about it being comparable to

the epidemic that started with long-acting OxyContin.

But going forward, if there is, for the data that they did compare Zohydro that didn't have abuse deterrence, but now there is an abuse-deterrent comparable hydrocodone on the market, when that was approved and it was approved compared to hydrocodone IR, how did its relative abuse deterrence compare to the data we are seeing?

In other words, if we go back into the record and look at that meeting, what was their relative change in liking thresholds or in extraction, et cetera? In other words, how abuse deterrent was that compared to this?

I know that's hard to do, but if they both used hydrocodone IR as a comparator, how does that compare?

DR. HERTZ: Are you asking about Hysingla?

DR. PERRONE: I guess. That's the only abuse-deterrent hydrocodone that has been approved that went through this process.

DR. HERTZ: I'll see if I can pull up the

label to show you what's in the current label, the package insert. But we don't have slides for you. I think that this is a challenge for us, as well, understanding the relative effects across different products.

Part of the challenge is when these get approved and when they're under development, they're not always timed so that we can get those comparators done. And I almost don't want to say this, but one can get a very general soft sense using when there are common comparators in cross-study comparisons.

But noting the amount of variability, noting that these tend to be smaller studies, I would caution any strong conclusions from cross-study comparisons. But we can get a little sense when there is a common comparator.

We'll try and pull up that label for you in some format so you can see what those results were.

DR. PERRONE: That's great. I guess the question is what do we do without a threshold to go by set by the FDA guidance? If we get some general

sense that that was approved with a 90 percent reduction in availability in some format and this is 50 percent or however you want to relatively -- then we'd want to continue to keep it at a 90 percent threshold, if that's possible, versus the any reduction equals abuse deterrence. I guess that's my concern.

DR. HERTZ: That's our concern, as well. And the lack of being able to come up with quantitative standards is, in part, because it's a constantly moving target now. It is still qualitative, for the most part, and I'm not sure that we'll ever get to a firm quantitative state.

It would be nice if we could have head-to-head comparisons of abuse-deterrent formulations, but I think we would potentially get stymied with all these different durations about to come in and then the next one prior was approved.

The staging of it could potentially grind it to a halt if we were constantly trying to -- I'm not entirely sure how to fix that, but I think your point is very well taken. But we'll try and get

that other info up.

DR. PERRONE: Thank you.

DR. BROWN: Dr. Morrato?

DR. MORRATO: This is a follow-up question that I think follows on the same conversation. In just looking at the figure -- for Dr. Levin -- Figure 2 and Figure 4 in the package, I'm not sure of the slides, slide 12 or 9. I was just going back to look at other labels with abuse-deterrent formulations. This looks to be a pretty standard graph.

But I'm just curious, given the conversation around focusing on take drug again, the thinking of the agency of this is a graph on drug liking. And I see bars that go at the 30th and the 50th and if there was any sort of thought on the FDA as to should we be directing our attention at rates that are at those threshold cut-offs and how we think about these data.

DR. HERTZ: Because a lot of these studies have primary outcomes that are drug liking, we don't want to ignore the statistical approach.

That's part of it. Part of it is this continuous responder-type analysis is one we've adopted for efficacy data, as well, the idea of having a fairly constant approach to showing results.

Thirty and 50 percent are simply common anchors for the purposes of giving one a place to focus, but unlike some of the work that's been done in some populations regarding what represents a clinically meaningful difference, for instance, in reduction in pain in certain pain populations, we don't have that kind of information here. These are just visual anchors.

DR. MORRATO: If I understand the first part of how you responded, since other studies have been statistically sized or powered based on the liking variable, their labeling followed from that or are you shifting in thinking that the take drug again is really the more meaningful one and we should be looking at a graph.

I don't know if you have the similar kind of graph for the other measure.

DR. HERTZ: You raise a lot of questions and

I think part of this is learning over time. We put in the data in terms of the tables. There are a lot of potential data presentations, the pharmacodynamic over time curves, the PK over time curves.

There's a lot of information that could go in. We're not entirely sure always of how much, so if you have thoughts about that. But most of what you're seeing, if we go back to the first product that had the labeling consistent with the guidance, we've been developing the guidance, we've been developing the approach to labeling over time as information has come in.

The more studies we get and the more we understand or get to evaluate results after, we're learning about the information. I think it's just a reflection, in part, of the newness of the field, trying to sort out what might provide clinicians with useful information, trying to avoid clutter of too much information, which can be counterproductive.

That's where we are. It's an evolution.

DR. BROWN: We're going to defer other questions until after lunch and we're going to stop now and take a break. We'll reconvene again in this room in one hour from now at 1:00. Please take any personal belongings you may want with you at this time.

Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any member of the audience. Thank you.

(Whereupon, at 12:07 p.m., a luncheon recess was taken.)

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

(1:01 p.m.)

**Open Public Hearing**

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

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA

encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully, and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 please step up to the podium and introduce yourself, speaker number 1?

(No response.)

DR. BROWN: Speaker number 2? Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. THOMPSON: Hello and good afternoon. My name is Edwin Thompson. I am the president of PMRS, Incorporated, located in Horsham, Pennsylvania.

I submitted a citizen's petition to the Food and Drug Administration on February 19th of this year, 2016, asking the FDA to revoke the abuse-deterrent labeling on OxyContin, retroactively revoke the three-year exclusivity given to OxyContin, and restore the original OxyContin NDA.

The scientific reasons for these requests are in this citizen petition. The petition was provided to you, the advisory committee, in my written statement submitted in advance of this meeting. My request is that you take the first step in stopping the opioid epidemic by applying the required scientific and legal principles identified in the citizen's petition before

approving additional abuse-deterrent labeling for opioid products.

The FDA should use evidence-based science to approve abuse-deterrent labeling. This requires that studies are scientifically rigorous, that the studies permit a meaningful statistical analysis, that they are reproducible, that pharmacokinetic and pharmacodynamic data correlate, and that they are in the best interests of patients.

I would like to bring to your attention three key issues and ask that you consider them in your deliberation and your voting. I am using the approval in labeling of OxyContin as an example so that you do not repeat the same mistakes in approving abuse-deterrent labeling for future products, including today's review.

Number one, OxyContin abuse-deterrent labeling was approved as a supplement for reformulated OxyContin on one and only one liking study, study OTR 1018.

In the FDA's own written words, no other data exists to support approval of this supplement.

Such an important decision and only one study.

In liking study OTR 1018, the FDA used only pharmacodynamic data to approve abuse-deterrent labeling for OxyContin. The pharmacodynamic data did not reach the required "meaningful statistical analysis."

The package insert states, "The intranasal administration of finely crushed OxyContin was associated with a numerically lower mean in median drug liking score and a lower mean and median score for take drug again compared to finely crushed original OxyContin or powdered hydrocodone hydrochloride," as summarized in table 4.

The pharmacokinetic data should have been required, and pharmacokinetic data and pharmacodynamic data must correlate to be reproducible and scientifically rigorous. You know that the PK data is valid data and reproducible.

In these advisory committees, you've been told time and again that the PK and PD data do not correlate. So the pd data is not reproducible. You know that liking studies, including this

study OTR 1018, are not scientifically rigorous and do not produce meaningful statistical analysis.

Liking studies are not valid scientific evidence and should not be a requirement for abuse-deterrent labeling, nor should they be used to approve abuse-deterrent labeling.

Let's look at table 4. The patients liked finely crushed original OxyContin over oxycodone hydrochloride powder. There's no better liking than oxycodone hydrochloride powder, none, but there is in this study. It's originally finely crushed OxyContin. This liking study design is flawed and this study is flawed, yet it is this single study that enables sales representatives to give hundreds of thousands of presentations to doctors to prescribe OxyContin with a margin of safety because of its abuse-deterrent labeling.

It produces three years of FDA-provided exclusivity from competition and prevents generic products from providing tens of billions of dollars of savings to consumers in pain.

Number two, abuse-deterrent-labeled

OxyContin provides no significant abuse deterrence to the primary known route of abuse, oral consumption. The FDA has stated that the vast majority of deaths associated with OC, original OxyContin, were related to oral consumption.

The approved labeling for OxyContin, what sales representatives are promoting to doctors, states, "Relative to original OxyContin, there is an increase in the ability of OxyContin to resist crushing, breaking, and dissolution using a variety of tools and solvents."

This statement is true, but it is highly deceptive and clearly lacks full disclosure. In the product labeling in table 4, it is reported that both original OxyContin and reformulated OxyContin are finely crushed, overcoming the resistance to crushing and breaking.

Also, it was reported by the FDA that reformulated OxyContin, when vigorously chewed, dose-dumps. The FDA review reported, "Upon chewing vigorously, ORF and OC products are bioequivalent with respect to oxycodone Cmax and area under the

curve. Reformulated OxyContin has no meaningful advantage in breaking and crushing over original OxyContin."

The FDA clinical review, summary of evidence and conclusions, included the statements, "The controlled-release properties of ORF, reformulated OxyContin, can be overcome with chewing and swallowing." Doctors should have been informed that the controlled-release properties of OxyContin can be overcome when finely ground and swallowed and chewed vigorously and swallowed.

This is more important information for a doctor than the information in the labeling. This information would prohibit rather than approve abuse-deterrent labeling.

Third point, the OxyContin label informs doctors that when subjected to an aqueous environment, OxyContin gradually forms a viscous hydrogel, for example, a gelatinous mess that resists passage through a needle.

The division director, Dr. Rappaport at the time, in his summary review, stated, "These

features also render the product almost impossible to dissolve, syringe, and inject."

Dr. Throckmorton, in his summary review, stated, "OCR gradually forms a viscous hydrogel, for example, a gelatinous mess that resists passage through a needle. The in vitro testing was sufficient to demonstrate that OCR, reformulated OxyContin, prevents oxycodone from being drawn into a syringe to any meaningful extent."

These statements are incorrect. These statements are equivalent to telling you that you can take the door off a prison cell and not worry that the inmates will have to cut through the bars to escape.

The fact is that when OxyContin is subjected to an aqueous environment, it can easily be extracted to high-purity and high-label clean by an unskilled person in minutes, with viscosity similar to water, drawn into a syringe, and prepared for injection.

OxyContin can also be extracted in a common solvent to high-purity and label clean by an

unskilled person and easily drawn into a syringe or converted into crystalline form for distribution and sale. Reformulated OxyContin does not have any meaningful abuse-deterrent properties to prevent extraction and injection.

Reformulated OxyContin's extended-release properties are defeated when ground or chewed vigorously, resulting in dose-dumping. The liking studies used to approve OxyContin abuse-deterrent labeling were not scientifically rigorous and did not permit a meaningful statistical analysis.

The study design is flawed and the study is flawed. Reformulated OxyContin is easily extracted, drawn into a syringe, and made available for injection at high purity and high-label clean by an unskilled person.

You can take a giant step in stopping the opioid epidemic by voting to revoke the abuse-deterrent labeling for OxyContin, restoring the original OxyContin NDA, and requiring all current and future opioid abuse-deterrent-labeled products meet the standards set forth in the guidance and in

the Code of Federal Regulations.

The studies should be designed to be scientifically rigorous, permit a meaningful statistical analysis for the study, and be in the best interests of patients. Doctors should have been given accurate and meaningful product labeling, including full disclosure so that they can make an informed clinical decision for their patients.

You, this advisory committee, have the power to make a significant contribution to stopping the opioid epidemic.

Thank you.

DR. BROWN: Thank you, Mr. Thompson. Speaker number 4, step up to the podium and introduce yourself.

DR. TWILLMAN: My name is Bob Twillman. I'm the executive director of the American Academy of Pain Management. I have no financial conflicts to disclose.

The Academy is the country's largest organization for pain management clinicians and the

only one that has, from its inception in 1988, consistently promoted a model of integrative pain management. This model recognizes the value of a variety of treatments, including not only medications and procedures, but also a wide array of non-pharmacological treatments.

Today, the United States is struggling to address two very complex and very costly public health crises, namely, opioid abuse and chronic pain. These two crises are similar in many ways and are linked by the key factor of the involvement of prescription opioid analgesics in both.

Policy-based efforts to address these crises must be as complex as the problems they attempt to solve, because simple solutions for complex problems often produce negative, unintended consequences that may be almost as severe as the problems they address.

Today, legislators, regulators, and healthcare professionals all find themselves challenged by the perceived need to address opioid abuse by limiting exposure to these medications,

while simultaneously providing appropriate access for people with chronic pain who have a legitimate medical need for them.

Ironically, it is, to a large extent, the use of these products in ways that are not intended by people who do not have a legitimate need for them that creates access problems for people with chronic pain.

The common response to this misuse and abuse of prescription opioids is the development of simple, unbalanced policy solutions that tend to restrict access to opioid analgesics across the board, thereby creating access barriers for people with chronic pain.

Solving both of these problems without creating a zero-sum game will require implementation of a variety of policy and technological solutions. We need not just one tool, such as guideline-driven prescribing restrictions, but a whole toolbox full of tools if we are to successfully address both of these crises.

One very important tool in that toolbox is abuse-deterrent opioid medications such as the one you're considering today. While we can imagine a future in which we have medications that relieve pain without creating the risk of abuse, I don't see that we're on the verge of this kind of revolution in the pharmaceutical industry.

Instead, we're left to develop incremental improvements on the abuse-deterrent products we already have, hoping to get closer to our goal with each one, while simultaneously staying a step ahead of the clever chemists who may be able to defeat the abuse-deterrent technology.

Ensuring access to opioid analgesics for people with a legitimate medical need requires that we continually improve the available technology, making these medications safer for those who abuse them, the vast majority of whom shouldn't be using them in the first place.

If we lose the edge with respect to abuse deterrence, we can expect to see policymakers instituting further limits on prescribing, tying

the hands of healthcare providers who are simply trying to give their patients what's required to relieve chronic pain.

The medication you're considering today represents the kind of incremental improvement I've been talking about. Prescribers need to have access to an array of abuse-deterrent opioid analgesic options and this medication incrementally improves one of those options, namely, extended-release hydrocodone.

Allowing this medication to enter the marketplace will not give us a new tool in our toolbox, but it will give us a better version of one of the tools we already have. Therefore, in the interest of and for the benefit of people with pain who require opioid analgesics to maximize their quality of life, I urge you to approve this medication with the requested abuse-deterrent labeling.

I also urge you to do this in the interest of and on behalf of the pain care professionals, who see people suffering with chronic pain and want

to provide them with the best pain care possible, but who may not be able to do so if they're denied the use of opioid analgesics.

Please help both people with pain and their pain care providers by approving this product.

Thank you.

**Clarifying Questions (continued)**

DR. BROWN: Thank you very much. The open public hearing portion of the meeting has now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as public comments.

But before we move on, we will consider some of the remaining clarifying questions that we didn't have time for before lunch. We're going to begin with the sponsor questions, and, Dr. Wesselmann, you had a question for the sponsor.

DR. WESSELMANN: Yes. I would like to know a little bit more detail regarding the post-marketing studies that are planned and that relates

to slide 74, abuse deterrence expected to be confirmed in post-marketing real-world abuse studies.

If you could, educate me a little bit more on what the endpoints are of those studies, what parameters will be measured.

DR. MALAMUT: Teva will conduct Category 4 studies to assess whether abuse-deterrent properties actually result in a significant and meaningful decrease in misuse and abuse and their consequences of addiction, overdose, and death.

DR. BROWN: Dr. Wesselmann, do you have any follow-up to that?

DR. WESSELMANN: Yes. What are the timeframes you are looking at to do these studies? And what would be a cut-off point, like an increase in deaths by what percentage when you would feel that the measures you put in place are not sufficient? I am trying to see what would be the policy relation to these measures that you are implementing.

DR. MALAMUT: We will be conducting the

post-marketing requirements, the FDA-mandated observational studies that address the points I made during my prior comment. And we will be working with the consortium of sponsors who are also participating in these studies.

We have not yet gotten into the detail that you request in terms of cut-off points for death and other things.

DR. HERTZ: The post-marketing studies are in the background material. I don't have the page number, because I have it in sections, but it was, I think, the last section in there. That describes -- there are two sets of requirements, with some sub-bullets.

DR. WESSELMANN: I read those and I was wondering what the cut-off points would be when an action would be taken. What is the threshold where you would assume that the precautions applied are not working or that that method applied here is not working? And I didn't see that in the material, but I might have overlooked it.

DR. STAFFA: This is Judy Staffa. I think

what you saw in the background was the group, the consortium of all manufacturers who make extended-release long-acting products who are participating in 11 studies, and I think that's what the sponsor was referring to.

In addition to that, each sponsor also has their own post-marketing required study to actually evaluate the abuse deterrence of their product in the community. A lot of our thinking on this -- again, we're still learning as we go since this is new technology -- is laid out in the guidance itself in terms of understanding what do we want to see from the point of view of formally required studies.

But knowing that there's often a lack of data out there, we also invite sponsors to submit anecdotal data, supporting data, anything that would help us to understand better what's happening once these products are approved. But in terms of a cut-off, I think what we're looking for is "meaningful reduction," and we're hesitant to put a number there, because as Dr. Hertz referred to, the

landscape is constantly changing.

DR. WESSELMANN: Yes. That is why I was wondering, because it's a moving target. Even if this drug would be abused a lot, there might be other reasons, like access to other drugs not available. On the other hand, if we don't see much of abuse of this particular drug, that might be because in the market, there are easier other drugs to be abused, because as long as opioids are around and we need them to treat the patients, there will always be abuse.

But what is used to be abused will always vary depending on what is available in the market at a given time. And that's why I asked that question.

DR. STAFFA: It's a great question. And that's one of the reasons we very closely monitor the utilization of new products as they become more available, because it is connected. People will abuse what is generally available.

DR. BROWN: Dr. Campopiano?

DR. CAMPOPIANO: Most of my questions have

been answered and I think what I have left is more appropriate for the discussion section.

DR. BROWN: Dr. Sprintz?

DR. SPRINTZ: Yes. The only statement I wanted to clarify was actually from Dr. Lee's presentation, on page eight, that talked about the top prescriber specialties. And it listed family practice, general practice, and osteopathy for 21 percent as the primary.

However, if you actually look at the graph, it talks about anesthesiology at 18 percent in pain medicine. And I guess I just wanted to make the clarification that, generally speaking, most likely the anesthesiologists who are prescribing hydrocodone ER are actually pain doctors in pain medicine.

But most likely, the data source defined them as their primary specialty as anesthesia. So I would say that, at least in prescribing hydrocodone ER, you've got pain docs that, if you actually combined them, would be about 28 percent, plus I'm sure there's a bit with the physical and

rehab, as well, that would be involved in that.

The data is not exactly descriptive of saying primary care is the largest prescriber.

DR. BROWN: Perhaps we can ask some of the folks from the FDA about that, because that's something I've wondered about. I don't know very many anesthesiologists anywhere that are prescribing extended-release anything. Do you folks have any clarifying statements about the percentage of anesthesiologists that are prescribing extended-release opiates?

DR. CHAI: This is Grace Chai, the deputy director for drug utilization in the Division of Epidemiology II. I'm not sure if this directly answers what your question is, but these are the physician's specialty as the prescriber reports to the AMA. This is what's linked to the prescription data. Was that what your question was regarding?

DR. SPRINTZ: I think a lot of times what happens is that when they gather this data, they generally ask what your primary specialty is. So, for a lot of these docs, their primary specialty

may be anesthesiology. However, their secondary specialty or sub-specialty is pain medicine.

They're lumped as anesthesiologists as a category, but really what they are, they're prescribing long-acting hydrocodone. They're, I'd say, almost wholeheartedly pain doctors.

DR. CHAI: That sounds correct. Thank you.

DR. BROWN: Thank you. Dr. Bateman?

DR. BATEMAN: My question has been addressed.

DR. BROWN: Dr. Chauhan?

DR. CHAUHAN: Hi, Cynthia Chauhan. I was concerned in the initial presentation that age, gender, and race were not addressed. And I'm wondering, as you go forward into the post-marketing, if you would be willing to use those to look at this, too.

DR. MALAMUT: Yes. In our phase 3 studies for efficacy and safety, we did break down by all of those demographics. Is there a specific question I can answer about that?

DR. CHAUHAN: I didn't see the break-down.

DR. MALAMUT: We can show that for you. Yes. I can tell you that, by gender, it was even for men and women. For age group, we broke it down by less than 65 years and greater than 65 years. And we did have more patients who were younger than 65 years.

By race, it was predominantly white, 73 percent white, 20 percent black, and then the rest were other races. And there was no difference in demonstrated effect or in safety across those demographics.

DR. BROWN: Are there any other clarifying questions for the FDA or for the sponsor prior to the time that we go ahead and begin working on it?

DR. KAYE: Alan Kaye. I have one question for the sponsor. I was trying to quantify the talk about intravenous deterrence with numbers. And there are slides that just say syringeability.

Is there a way to quantify? I know you probably can't give an exact number, but just something to give me a little more precision.

DR. MALAMUT: Around our Category 1

syringeability data, is that your specific question?

DR. KAYE: Yes. I know it's not going to prevent 100 percent ability to inject it intravenously. But would you say it's -- I won't give you the number, but could you just give me something, just a little more that I could live with?

DR. MALAMUT: Sure. Allow me to call Dr. Moe back to the microphone to address that.

DR. KAYE: Thank you very much.

DR. MOE: Hopefully, this is what you're looking for. This is the extraction data. This is after the manipulation and after the syringe, so then we recover however much we were actually able to get through the syringe. Then we analyze that, 4 percent drug.

Here we have, again, always versus Zohydro for the two tools. It's about a fifth of the drug we were able to get out. The rest of it was lost to the thick viscous or to the filter.

DR. KAYE: Perfect. Thank you very much.

Thanks.

DR. MOE: Thanks.

DR. BROWN: Dr. McCann?

DR. McCANN: I have a follow-up question. As far as the viscosity data, was it room temperature or body temperature? Do you remember, Dr. Moe?

DR. MOE: The viscosity under which conditions?

DR. McCANN: When you tried to inject it through the syringe.

DR. MOE: Yes. Actually, what we would do is -- these are methods, so let's see. A typical method for an abuser is actually to boil or near that. I have to be careful.

DR. HERTZ: Was it explored under different temperatures?

DR. MOE: Pardon me?

DR. HERTZ: Were the conditions explored using different temperatures?

DR. MOE: They were explored during different temperatures and the viscosity --

DR. HERTZ: For syringeability?

DR. MOE: For syringeability, yes. And the viscosity is always quite high.

DR. McCANN: My follow-up question is I presume a determined abuser will find some way to inject it in. And at one point, I think you said that the drug with the polymers was somewhat like chewing gum.

Have there been any safety studies that have looked at whether that just mechanically is safe to abuse?

DR. MALAMUT: We didn't consider it safe to subject humans to injecting the manipulated drug with polymer. We have not conducted those studies in humans.

DR. HERTZ: This is Sharon Hertz. I think there can be a general assumption that if somebody manages somehow to force a gelatinous material through a needle, they're going to end up with an embolic type of phenomenon.

We don't typically require non-clinical studies to demonstrate that. In this setting, we

would never allow a clinical study. But typically, in that context, we would just assume it wouldn't be safe to do that if they had managed to get it through a syringe and a needle.

DR. MALAMUT: If the chair would allow, we did have a question from before the break.

DR. BROWN: Absolutely.

DR. MALAMUT: If that would be okay. We did have a question that we wish to show some slides on regarding standard error for PK and PD data. Mary Bond, can you review those slides?

MS. BOND: Yes. Mary Bond, clin pharm, Teva Pharmaceuticals. I know before the break, there was a request to look at the variability in the time course curves, and we shared the standard deviation. But clearly, standard error was of interest and so we wanted to also share those plots of the time course with standard error.

That is demonstrated here for our time course for liking for the oral study. We have that, as well, for the intranasal study.

DR. MALAMUT: Dr. Morrato, I believe you had

raised the question.

DR. MORRATO: It was Dr. Walsh, but this is very helpful. Thank you.

DR. MALAMUT: My apologies. Dr. Walsh?

DR. WALSH: Thank you for presenting those. Can you just go back one moment and show the intranasal data again? They're just flipping a little too quickly for me.

MS. BOND: Yes. I believe we had discussed the PK. Did you want to see those curves, as well, with error?

DR. WALSH: Sorry. Can you repeat that?

MS. BOND: I believe we had also discussed the PK data. Did you want to see those with errors, as well?

DR. WALSH: Sure.

MS. BOND: Again, first, oral, and I can move to intranasal, if you'd like.

DR. BROWN: Any comments?

DR. WALSH: I'd just ask one more question about those data. Do you have any figure prepared that illustrates each subject score as an

individual dot so that we can see distribution? Do you follow?

DR. MALAMUT: No. No, we don't have that curve prepared.

DR. WALSH: Thank you.

DR. BROWN: Are there any other questions, clarifying questions, for either the FDA or the presenters from Teva before we go on to Dr. Hertz's charge to the committee? Dr. Morrato?

DR. MORRATO: Let's see if I got it right. It's the follow-up question that, I think, Dr. Bateman was asking. The FDA is looking at some of the in vitro data and whether or not it's supporting oral and so forth. I wonder if the company has any comment on the FDA statement that there's not enough sufficient evidence to support any significant abuse deterrent by oral route or its superiority over the comparator extended-release.

DR. MALAMUT: Yes. We believe all our data does show oral abuse deterrence throughout Category 1, 2, and 3 studies. And the point, just to

reemphasize, that Dr. Moe made earlier is that in our Category 1 studies, we did test to failure, per the FDA guidance.

In that regard, it's not surprising that we were able to find certain combinations of multiple stress conditions that could overcome our abuse-deterrent properties. I'd also add that we didn't find many methods that could overcome it. Again, along with the message you've heard, our goal is to be abuse deterrent, not abuse-proof.

Again, just to reinforce, our Category 2 and 3 oral abuse-deterrent data did show significant results.

DR. BROWN: Any other questions?

(No response.)

DR. BROWN: If not, Dr. Sharon Hertz will now provide us with the charge to the committee.

**Charge to the Committee**

DR. HERTZ: Thank you all for your attention with the clarifying questions so far. As we proceed on to the questions that we have for you, I just want to present a few concepts for your

consideration as you go forward.

We recognize that because these products are analgesics, they have to be able to deliver the opioid. At the end of the day, there's always going to be some potential for abuse, even if it's by taking the product orally. Abuse deterrent, as we've said a couple times today, is not abuse-proof.

We as an agency accept that there is an overall public health benefit for incremental improvements in the development of abuse-deterrent opioids, but, also, as we've said, it's qualitative at this point and that's a challenge for all of us.

We have our guidance, which does describe that for these products, when the pre-market data show that a product's abuse-deterrent properties can be expected to result in a meaningful reduction in that product's abuse, the data may, together with an accurate characterization of what the data means, can go into the product labeling.

We think it's important to have a relevant comparator and I think we've also touched on

briefly so far that that's a challenge over time as new products come on the market while other products are under development. So the context of what's relevant changes and can be hard to chase for any given product's development.

The standard against which each product's abuse-deterrent properties are evaluated will depend on the range of abuse-deterrent and non-abuse-deterrent products on the market at the time of the application. That's also part of what our guidance states.

We have a number of reasons for why we don't approve products. They include problems associated with the control, manufacture or chemistry; the manufacturing facilities; inspection-related problems at facilities or clinical sites; concerns about efficacy labeling; PK data; non-clinical data; if the application contains untrue statements of material fact; does not comply with relevant regulations; if the rights or safety of subjects were not protected; if there is a lack of substantial evidence for supporting the product in

terms of efficacy or safety or if it's not adequately conveyed in the labeling.

What you may hear is missing from what our regulations currently describe are the kinds of comparative pieces that I think some folks want to have. There is no current regulation or requirement for there to be an incremental improvement to be better than.

We can consider potentially risks that may be greater, if there aren't advantages to off-set those risks, but a lack of being better is not currently part of our criteria for not approving a product.

As we go into the questions today, we're going to ask you to discuss your understanding or your conclusions on whether you think the data support abuse-deterrent properties for this product by various routes, and we're going to ask you to do a series of votes.

Every time we come to AC, we try really hard to learn from the past one in terms of clarifying the questions. If there are questions that you

need additional clarification or need to explore, please, I know you'll let us know. And I'm going to turn it back over to Dr. Brown.

**Questions to the Committee and Discussion**

DR. BROWN: Thank you, Dr. Hertz.

We're now going to proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Our first question is, please discuss whether there are sufficient data to support a finding that Ventrela ER, hydrocodone bitartrate extended-release tablets, has properties that can be expected to deter abuse, commenting on support for abuse-deterrent effects for each of the three possible routes of abuse, oral, nasal, and intravenous.

Are there any questions or comments related to the wording of this question put before the panel? Dr. Campopiano?

DR. CAMPOPIANO: I guess you would call this a wording question. We have an item to vote on later that goes to the pain indication. Do we have a discussion opportunity for that or do we just discuss it before we vote on question 2? The discussion question is limited to the abuse-deterrent properties and then we're asked to vote on the pain indication.

DR. BROWN: We will, in fact, have an opportunity to discuss each individual question as it's presented to us.

Clarifying comments, questions about this? And I want to make certain that everyone around the table, whether that person be a non-voting or voting member of this group, has an opportunity to offer their input. Dr. Emala?

DR. EMALA: I'll start off the discussion particularly about the oral aspects. Coming back to the questions I raised this morning, the sponsor has suggested that they pushed the product to the limit of failure. But I think that the data presented during their presentation, as well as in

the briefing document, with a solvent that is widely available to a potential abuser, with a tool and conditions that seem fairly easy to perform, that I'm not convinced that an appreciable amount of drug could be readily extracted for oral abuse in a solvent that would be quite compatible with that.

Do you want to talk about all three methods or do you want to go one at a time? The nasal abuse, I was impressed, did have some deterrent properties both because of viscosity issues and some of the Category 3 studies. I'm particularly focused on the early 30-minute kind of effect in the Category 3 studies, where I was impressed that the drug liking and such seemed to be much less at the 30-minute time point.

To me, looking at later and later time points seems less applicable, because a potential abuser, I think, is looking for an early, quick high by these alternative routes. And I was fairly convinced, from an intravenous standpoint, that it would be a very difficult formulation to use by

that route, as well.

DR. BROWN: Dr. Walsh?

DR. WALSH: I'm going to skip to the intranasal data. And I think that I'm less impressed with the intranasal data, to be honest with you. If we are reliant only on the primary outcome measure of difference in Emax, the difference for the primary comparator is only about seven points, whereas the difference for the oral study is much larger. And we do have available data from the other drug that's on the market as a hydrocodone extended-release that has intranasal abuse-deterrent labeling. In that case, the different score is closer to 25 points.

That's a really substantial difference compared to what we're looking at here.

While I agree that users are generally looking for a more rapid high, the reality is that it's been hard to demonstrate that relationship, a really tight relationship between the PK and PD for opioids. It is clearer for some other drug classes. And opioids are not really short-acting,

generally, not the ones that people want to abuse.

I think shifting the Tmax is important, but I wasn't impressed overall with the shift in Cmax or Tmax for the intranasal data. I'm fairly convinced, because I work with people who abuse opioids regularly, that the viscosity of the product will deter intravenous administration.

DR. BROWN: Any comments about oral administration of Ventrela?

DR. WALSH: I appreciate what Dr. Emala said about if you press hard enough, you can get anything out. But herein lies the rub, that we want the drug to come out for the people who need it. That's always going to be the case.

I think that the Category 3 study with the oral administration made me believe that there would be some deterrence or at least there would be certainly less preference for this product over others that are on the market.

I'm not certain how the magnitude of difference maps on to the magnitude of difference for the outcome measures that we're relying on for

the other six marketed products.

DR. BROWN: Yes?

DR. EMALA: Could I just follow-up to that? The comment about the Category 3 for the oral, it was done with a manipulated formulation, but not an extracted formulation. And I think that gets into some of the language we were talking about earlier, where Dr. Bateman pointed out that the language in the briefing document talked about the pure in vitro data not supporting deterrence from oral abuse, whereas the FDA suggested if you combined the in vitro and the Category 3 data, that there was.

But I think there's a little apples and oranges being compared of the manipulated crushed product to an extracted product, again, in a solvent that's widely available.

DR. BROWN: Dr. Shoben?

DR. SHOBEN: Just a couple of comments. One is to say that I think that there is some sort of abuse deterrence for the oral just because of the nature of the crushing not defeating all of the

extended-release properties. That is an improvement and that was what was backed up in the Category 3 studies.

It certainly means that it could be defeated. These extracted comparisons and things, of course, you can defeat it. But I think there is an incremental improvement, in a sense, in terms of someone who accidentally crushes their pill or the easiest methods for oral abuse. There is some level of deterrence.

It's not perfect, obviously, but I think there is enough there for me to think that there is a deterrent there.

I would agree with Dr. Walsh that the nasal data is a little less compelling, although I would certainly caution these comparisons of these Category 3 studies across the studies. They're very difficult to compare across Category 3 studies early, or so I was told last time, so it's kind of hard to know.

It was modestly superior to the competitor that they chose. That's not the current status and

I don't know how that should be weighed. And I would agree with everyone that the intravenous, the gelling seems pretty compelling.

DR. BROWN: Dr. Campopiano?

DR. CAMPOPIANO: I have a broader question that I think goes to abuse deterrence. And I think I'm going to preface it by saying it's not really a direct comment on this product or the sponsor's approach to analyzing the effectiveness of this form of deterrence.

It has more to do with more the broader discussion about how we are looking at what the comparator should be. And I totally understand the thinking that you would compare a hydrocodone-containing product to a hydrocodone-containing product.

But I'm just wondering what people, especially those of you who have been through this process for a number of abuse-deterrent products, think about. From the prescriber point of view, if I'm deciding what product to prescribe, I might be comparing a hydrocodone product to another

hydrocodone product.

But from the drug user's side, I'm going to be comparing this product that I happen to get my hands on to whatever is most readily available and it's not necessarily going to be another hydrocodone product. There are drug users who have preferences for certain categories of opiates.

But I'm thinking that as we explore what does it mean to be abuse deterrent, how many eggs do we want to put in the basket of comparing head-to-head competing-in-the-market products versus competing-in-the-substance-user's-world products? It's more just a question for everybody's consideration.

DR. BROWN: Can I speak to that, because I have an interest in that very thing. And based on what I can determine, we don't know that now. We don't have this marketing data that's going to demonstrate to us who is the most effective and who is not the most effective, nor do we know what to do about it when we figure that out.

We're largely going on the basis of each

individual product considered as its own standard rather than as a standard against another product right now. Dr. Gerhard?

DR. GERHARD: Toby Gerhard, Rutgers. I would like to broaden the discussion even more, I guess, unless FDA objects. I think we have to think just --

DR. BROWN: Can I just interrupt for just a second and say we want to try our best to limit the discussion to this particular drug. If we do not, we will not be able to give the FDA the information that they require to act on this particular drug.

There are larger objectives and I'm certainly aware of those, but we need to move down the road with this drug.

DR. GERHARD: I'm happy for you to just -- let me, please, just state the question and then maybe you can react. I think it applies certainly to this product, not exclusively to this product, but I think we should consider the question of unintended consequences of granting an abuse-deterrent labeling to opiates.

We should think about the potential downside of doing that and whether we are giving or lowering the bar of prescribing long-acting opiates in general by providing this, in a sense, marketing tool of abuse deterrence and giving the impression that these drugs might be safer generally beyond that.

I think it is an important point, though not specific to this one. I don't know whether there are comments or whether you consider this in scope or out of scope.

DR. BROWN: Dr. Choudhry?

DR. CHOUDHRY: I'm not going to address Dr. Gerhard's comments, if you don't mind. But I think one of the things we struggled with a lot -- briefly, I think he does make a very legitimate statement.

One of the questions that we struggle a lot with is what constitutes a good outcome or what outcome measure is good enough.

The guidance that we got before arriving here and certainly the charge to us was that it's

the totality of evidence. And I think that's a reasonable approach when there isn't a single outcome that we think to be acceptable nor a level.

I think my overarching comment is really around the need for better data. We need to be able to begin to predict abuse and/or average use, whatever you want to call it, better.

One clear recommendation I think that we can offer as a committee is a charge to the FDA to help foster the science here for us to figure out which of these metrics we should be using.

I agree that some of the PK data, especially for the intranasal stuff, is a little less than compelling. But I am intrigued by the take drug again kind of data. And at least one crude way to figure out whether the differences are clinically meaningful or not is to compare the differences between the groups and relative to their standard errors.

We see that in percentage points between the groups, for example, either with intranasal or the oral abuse studies, the differences in percentage

points are 6 to 7 percentage points, which is 2 to 3 times the standard errors that are presented.

Generally, that would constitute something that we might consider to be clinically meaningful. On balance, forced to make a decision, I do find this actually compelling enough, but ultimately, I think our recommendation really needs to reflect the idea that we actually need to know which of these outcome measures does correlate with longer-term abuse.

DR. BROWN: Dr. Morrato?

DR. MORRATO: I agree with Dr. Choudhry. My comment is similar, and I'll try not to repeat exactly. Just reflecting, each one of these meetings sets a precedent for future meetings. And I think this is a set of data in which you do see consistencies in the measures, across measures. You see separation of placebo, unmanipulated, with manipulated versus control. And you see that evidence across the types of categories of studies, the pharmacodynamic, pharmacokinetic, and in vitro.

Now, that doesn't mean that with

manipulation, you cannot overcome some of the barriers, but it's at least a package in which we're now seeing all of those measures in terms of a hierarchy of evidence. Prior drugs sometimes may just show one or a piece of it.

In this case, I think we're seeing more consistency. But again, this is the nuance to think what Dr. Gerhard is trying to get at in the unintended consequence of what does it mean to say you're an abuse-deterrent claim and splitting hairs with abuse proof and what messaging actually goes out.

Ultimately, what's the value of having an abuse-deterrent claim from a business sense if someone can still claim they have abuse-deterrent physiochemical properties versus a labeled FDA claim? And I hope that the FDA is also monitoring not just the data side of it, but the marketing side of these kinds of claims and perceptions that patients or physicians might have about different drugs based on what's really a labeled claim or not, because we could be arguing over the data

when, in essence, in the market, it's not very differentiated.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: A number of people have said no opioid formulation is going to be abuse-proof. The question then becomes how hard it needs to be to extract large amounts of the opioid, as well as how large the reductions in the PK and PD measures for the physically manipulated drug need to be before we can conclude that the formulation is likely to result in a reduction in abuse liability.

I think we really don't know how high this bar needs to be. It's ultimately a very subjective decision in the absence of data. I, too, would put in a plea for more data to inform these questions. And I'll look forward to the data that's emerging out of the post-marketing surveillance studies for the currently available abuse-deterrent formulations and helping us with these questions in the future.

DR. BROWN: Dr. Gerhard, did you want to follow-up? I'm sorry. I didn't mean to cut you

off, but did you want to follow-up on any of your comments that you made prior?

DR. GERHARD: No. I just forgot to put this down. But just generally, I agree completely, to the question, with most of what has been said, that this product specifically certainly showed a lot of improvements on the direct question of abuse deterrence. I think I agree with most of what's been said here.

DR. BROWN: Dr. Kaye?

DR. KAYE: I just wanted to comment that I was here when Zohydro ER -- we had a very lively discussion, and when you look at slides 39, 41, and 43, back then, we were saying give us something versus nothing. And now, we're debating that bar, and I think it's very positive. And I think this committee and the FDA is really going in the right direction.

DR. BROWN: Dr. Perrone?

DR. PERRONE: I'm sorry. I didn't understand exactly what you're saying. Are you saying --

DR. KAYE: I'm saying we're getting there slowly rather than not getting there.

DR. PERRONE: Getting where?

DR. KAYE: Getting to a world where these drugs have a safeguard. I'm not saying how much of a safeguard, but at least we're getting there.

DR. BROWN: Are there any other questions or comments concerning this particular question?

(No Response.)

DR. BROWN: If not, I'm going to read the question again and then summarize what I think I've heard.

Please discuss whether there are sufficient data to support a finding that Ventrela ER, hydrocodone bitartrate extended-release tablets has properties that can be expected to deter abuse, commenting on support for abuse-deterrent effects for each of three possible routes of abuse.

Before getting to that, let me say that from the comments of a number of the members of the committee, there are still general questions about what is the meaning of abuse deterrence, the

meaning of past recommendations that have been made by this committee relative to abuse-deterrent properties.

That being said, it appears that the committee's belief, for the most part, is that the data that was presented for all three of these routes of administration do show at least a modicum of reduction in the possibility of abuse and that though it be incremental, that at the present time, is compelling.

Any comments to my comments?

DR. SPRINTZ: Michael Sprintz. I do have a question. In question one, then, it's either a choice of agreeing with all three, all three at once, or can we agree with two or one as opposed to it's either all or nothing?

DR. HERTZ: No. This is a discussion point. Sorry. This is Sharon Hertz. And as you'll see later on, we'll actually give you the opportunity to vote by route. The last three questions would be about if there should be something in the label to support oral, IV, nasal separately.

DR. SPRINTZ: Okay. The only other thing I did want to say is that I did want to echo what Dr. Gerhard said in regard to being cognizant of the unintended consequences of how we label these down the line in terms of abuse in marketing and how it would be presented.

DR. BROWN: Thank you. If there are no other comments, we can go on to question number 2. And this is a voting question.

Should Ventrela ER be approved for the proposed indication, management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate?

Are there any questions or discussion prior to the time that we come to a vote? Dr. Perrone?

DR. PERRONE: Jeanmarie Perrone. In going along with the CDC opioid prescribing guidelines that had some considerations and concerns about prescribing opioids for chronic pain with frame of reference in terms of who really benefits from that and what the outcome should be in terms of return

to function or who really gains a long-term benefit.

We were looking at this specifically in the management of pain, and the only pain outcome we saw, I believe, was related to self-reported improvement in pain. What concerns me about going forward is that we set precedence at these meetings where all we have to do is approve it the way the other drug got approved.

When are we going to change our requirements that we actually need to show some improvement in pain and other outcomes that are actually relevant to the patient in terms of gain in function? This is really how we got here. Right?

Everybody's pain got better. All of our pain would get better. But did we get better in the big picture? Did we actually get a better life, get back to work, get back to our families, get back to our ADLs? And that's really where we are. And I know this might be out of the frame of reference of where we are, but you're asking me the question about should it be approved for pain and

we're trying to set precedence related to the next drug that comes along.

My concern is we have 10, 15 drugs on the market, whether they're abuse deterrent or not, there is just more drugs out there and we don't even know what we're using them for, whether there's abuse deterrence or not in terms of a real indication.

That was a teeny tiny part of this meeting, but it really concerns me to go forward and say this is a good drug for pain, when maybe none of these drugs are good drugs for pain in the large number of people who have been prescribed them. It's a message to clinicians and it's a message to patients and patient expectations around pain management.

DR. HERTZ: So I'm not going to let you off the hook with that without a little more, please. I think that part of the complexity of this was captured by your statement, which is what are the functional outcomes then that you think should be required to change when you talk about improvement

in function, because this is something that we struggle with.

What constitutes an improved function in a pain population? Is it return to work? Is it emotional functional improvement, functional improvement in ADLs, functional improvement within the family structure, functional improvement within the community?

That's part of the challenge, knowing how and what to measure, because to show improvement, one must show a deficit. Should we be only enrolling people who have pain sufficient to cause a lack of function so that we then have an opportunity to show an improvement in function?

How do we differentiate that from people who have pain and are functioning at some level?

I don't disagree and there's been much discussed about this over time. You have good perspective, having been here for a lot of these meetings.

What do you think then should also accompany this that would help you with regard to some of

that, some of what you've raised?

DR. PERRONE: Thank you. Jeanmarie Perrone. I think we can't accept just self-reported pain score improvement and that we need to pair it with very many of the pain functional outcomes that you just discussed, return to family, return to ADLs, possibly return to work, maybe not exclusively one of those things, but a composite, which I believe there are functional pain score or functional outcome scales that studies use to measure those things.

I think pain doctors maybe could comment on what they use to get people back to reporting that their pain has improved.

This is what the pain people in our organization do. They make them fill out various assessments of other things that are going on in their lives that have improved or they take them off the opioid, in the more aggressive pain management practices.

DR. HERTZ: Basically, we should only study these in patients who have functional deficits, is

that part of what you're saying? I don't want to read into it. That's why I want to clarify.

DR. PERRONE: I'm not sure who we should study it in, but I think that we need to have outcomes that make sense beyond self-reported pain score. I just think that that's really how we've gotten into this and this is why we need different criterion.

If some of these people were on 90 milligrams twice a day in a 12-week escalation, that gets to be a lot of drug for people, that the only outcome has to be, "My pain got better." Your pain is going to maybe get better, but you're going to need increasing drug to maintain that over time in most people, and that's not a very good outcome.

I wonder how many people went on to have opioid-dependent chronic pain forever after being initiated on this drug. We can't ask those questions, but that's part of our problem with this epidemic.

DR. BATEMAN: Can I make a point along those lines? I think another issue is that the trial is

only 12 weeks in length, and we know opioids, at first, can work, but over time, tolerance develops and patients start to develop side effects from opioids.

I think, in the future, I'd certainly like to see much longer trials to establish the efficacy of chronic opioid therapy and opioids that are being proposed.

DR. BROWN: Ms. Chauhan?

DR. CHAUHAN: Cynthia Chauhan. I agree with Dr. Perrone's concerns. There's a whole bank of quality of life and patient-reported outcome forms that are very specific and address very specific issues. I think engaging those in these trials would be a very helpful thing and bringing in quality-of-life expertise to the discussion.

It's a well developed area that I think has very strong implications for this. And I think you're right. As you move on in chronic pain, sometimes the amount of medication you need changes and your ability to maintain your quality of life fluctuates very much.

I think that's a very important issue to look at.

DR. BROWN: Dr. Besco?

DR. BESCO: I guess I'll just kind of build upon the statement, what is being talked about now. But I've been sitting here today and just kind of thinking about what the actual clinical need is for this product in the community, especially since there's really no shortage of alternative extended-release products available today.

To me, it doesn't really take a scientific study to conclude that if a product like this isn't available, then the public can't misuse it or abuse it. I also could see that this would be very cost prohibitive for patients that would actually benefit from it. Just some additional comments about practicality of the product.

DR. BROWN: I want to try to get us back on track here. As I said before, we are here today to consider this one drug. And while the comments and questions that have been asked are very important and I honored those, we need to deal with the

question at hand, which is should we recommend that the FDA approve Ventrela ER for the proposed indication, management of pain severe enough to require daily, around-the-clock, long-term opioid treatment. Dr. Choudhry?

DR. CHOUDHRY: I agree wholeheartedly with Dr. Perrone and the idea that we need different outcome measures. That said, if we look at the indication we're looking at -- and I think, Dr. Brown, you're partly getting at this idea -- we're looking at the indication for the management of pain, although the outcome we really care about is functional -- or one of the outcomes we care about is disability, and ADLs, and functional return or preservation of function.

Pain is also an outcome that's of relevance. I have some direct experience in pain. And to that end, at least in the industry's briefing documents, in table 9, the outcomes in the clinical outcomes efficacy studies, which are the only two that we really have to go on to speak to this, 3079 and 3103, the primary efficacy variables were both

pain-related and the rationale that's stated is that this is the U.S. FDA preferred primary variable based on end-of-phase-2 meeting minutes.

To some extent, there's a moving target problem here, out of fairness. To the question of whether or not this actually improves pain, the answer may well be yes, and that's what the industry was asked to demonstrate.

Should we know that it improves other things, as well? Absolutely. And perhaps one of the things we could do is require that those sorts of studies be done.

DR. BROWN: Dr. Morrato?

DR. MORRATO: Yes, thank you. Elaine Morrato. Just to cap the conversation, I was wondering if the FDA might give us an update. I know one of the points in responding to the prescription opioid epidemic in the U.S. that was laid out by the commissioner or others was this discussion around developing a better evidence base.

It was mentioned in the article that the

Department of Health and Human Services, and agencies, and the FDA are developing a program for mandated industry-funded studies and a coordinated plan for conducting research that will answer some of these questions that we've been talking about in order to guide opioid use.

I was just wondering if there is any update on the status of that planning activity.

DR. HERTZ: I can tell you there's a lot of discussion going on internally. I don't have a lot that I can report out right now. We've discussed in some other contexts -- and I don't want to get too far into it right now -- some of the challenges with longer studies. Trying to keep somebody on a placebo who would otherwise warrant an opioid for an extended period of time or something else that's less effective is very difficult to do.

People drop out and then we have missing data problems. We're looking at some other study designs, but it's a big challenge. What I will point out, though, is that even though these are often 12-week studies, many times, these are

patients who have already been on opioids for an extended period of time.

We're not testing them de novo always for 12 weeks. They're people who have been on opioids for sometimes quite a long time before enrolling, and then we're testing the efficacy of this opioid in that study of those patients.

It's not the kind of controlled extended period, because even the non-opioids that are approved for chronic pain or pain-related indications, like osteoarthritis, rheumatoid arthritis, the neuropathic pain conditions that have them, are also based on similar duration studies, because the feasibility of extended controlled studies is very challenging not just with an opioid, but in the whole area.

We're working on that, because one might almost argue that if we kept these people in the study for a year and half of them stayed on placebo, perhaps we enrolled the wrong group of people because half of them managed on placebo for a year, even with little rescue. Then it would be

argued that that's not even the right population to study.

We're sensitive to the importance and we're working very hard to sort out what that could look like for the purposes of providing better support for this.

I'm listening carefully to the interest in the other outcomes, but there are other challenges and we're not going to give up trying to help provide more data to inform when this chronic use has -- well, to inform the question that's been put out there.

DR. BROWN: Dr. Campopiano?

DR. CAMPOPIANO: I feel like I'm coming out of left field, but it goes a little bit to what is the message we're sending. And the efficacy studies for pain relief, I was a little -- given the amount of guidance in family medicine and in general practice about low back pain and the use of opiates for low back pain, I was a little surprised that I was confronted with making a decision about recommending an effective opiate for low back pain.

I realize that's not the indication, but that is the diagnosis that was chosen to put there. We're looking at pain relief in a condition that, in clinical practice, you're not supposed to use opiates to treat.

I thought, okay, well, what message is that sending. And then you're looking at a product that has special labeling for abuse deterrence, but I don't see where those added properties, that appear to be quite benign, did we look at what is the person with pain. If I'm just saying to my patient, "I can provide you this old hydrocodone product or I can provide you this new hydrocodone product that's abuse deterrent," they're going to say, "How is it going to be different for me?"

I can say, "Well, it looks like it's going to relieve your pain about as well as the old one does," but I can't tell them anything about any side effects, because what was presented was compared to placebo, which is standard practice.

But now I'm trying to make a decision between two different drugs with different

properties, one of which has special labeling because of the properties, and I can't tell the intended patient that I need to treat what the impact of those properties might be on them.

I just feel like I'd be putting my colleague out there and his or her patient sitting in front of them and they'd go, "Well, it's for the social good. It's for the benefit of the health of the public that we put these extra features in your drug. I can't tell you whether you're going to be more constipated, have more stomach upset, or what. I can't even begin to speculate."

I just feel a little concerned about stamping it approved and then putting it out there with some kind of major unknowns when it comes to what does the patient that this is intended for need to be told about this drug and what should their provider be prepared to tell them, on top of the concerns I already shared about what do we really know about its abuse deterrence.

DR. BROWN: Dr. Besco?

DR. BESCO: I'm sorry.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: I agree that the pivotal study 3103 that looked at the efficacy showed a reduction in the increase in pain scores associated with treatment. But I think it's worth noting that the difference in the pain scores, the primary endpoint between the drug and the placebo were only 0.6 points on a 10-point Likert scale.

That's a very small amount of improvement, I think, and perhaps the general public and clinicians don't realize how small the effects are, particularly given all the harms associated with these medications.

DR. BROWN: Dr. Sprintz?

DR. SPRINTZ: Thanks. Mike Sprintz. I definitely agree with what a lot of people have already shared, especially what Dr. Brown brought up. And one of the challenges that I find is, in both practicing pain medicine and addiction medicine and when we look at pain, here at the FDA, we're evaluating a drug.

When we look at the treatment of pain, it

really ideally should be an integrative, comprehensive approach that addresses both the physical aspects, the psychological aspects of pain, not just one or the other.

When we look at comprehensive, when we start to measure outcomes of quality of life and functional improvement of relapse prevention or to decrease the probability of progression of addictive disease, it is very complex.

Adding all those things in, in terms of long-term studies, I think, is challenging when we look at it from the pharmaceutical standpoint, because, in essence, I'm being asked to evaluate a drug for treatment of pain, but it's not this absolute in this vacuum, because an opioid is one of the things that we would use as a means of managing moderate to severe pain in a patient, in addition to physical therapy, complementary therapy, psychological therapy, interventions, and other medications that may be non-opioids or have low abuse potential.

I say all of that to really make it clear

that that's one of the big challenges in defining, okay, this solves pain, because it's much bigger than that. And I think moving forward, a lot of the suggestions here were really, really important moving on, as we start to change the way we look at pain and how we evaluate pain treatments.

DR. BROWN: We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote.

If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen.

The DFO will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the

reason why you voted as you did, if you want to.

We will continue in this same manner for all questions until we have gone all the way around the room. So if you would, please, press the button on your microphone that corresponds to your vote. We'll have approximately 20 seconds to vote. Please press the button firmly.

After you've made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

DR. BEGANSKY: The vote was 14 yes, 3 no, zero abstain.

DR. BROWN: Everyone has voted. The vote is now complete. Now that he vote is complete, we'll go around the table and have everyone who voted state their name, their vote, and if you want to, you can state the reason why you voted one way or the other.

I think we're going to start with

Dr. Wesselmann.

DR. WESSELMANN: I voted yes because I --

DR. BROWN: Please state your name.

DR. WESSELMANN: Ursula Wesselmann. I voted yes, because I was impressed by the data that were presented to us, especially for the IV preparation. I think there is only modest evidence for the nasal and oral route. But we voted it as one package. It is a drug that is already on the market and I think it's the right step forward to package it in an abuse-deterrent preparation.

DR. GERHARD: Toby Gerhard, Rutgers. I voted no. It was very close for me, a very difficult decision in the end. Dr. Perrone's comment really pushed me to the no vote. I completely agree that it's somewhat inconsistent certainly when compared to any other extended-release opiate on the market.

This product isn't any worse and, in that sense, should be approved. However, if we don't start to rethink how we approve and regulate opiates in general, long-acting opiates

specifically, I think we'll never kind of really change the problems that we have with the opiate epidemic. And I think comments regarding the abuse-deterrent properties come later.

DR. HIGGINS: Jennifer Higgins. I voted yes, and largely because I want there to be greater options for consumers.

DR. CHAUHAN: Cynthia Chauhan. I voted yes. I think that it's a small step, but an important step. And I think there are a subset of patients we haven't discussed who will not take the appropriate opiate because they fear addiction. For those patients, something like this helps them move past what may, in that case, be an irrational fear.

DR. SPRINTZ: I'm Mike Sprintz. I voted yes. I really struggled with this and it was a hesitant yes, because everything that we've been discussing in terms of how things need to change in relation as to how we define pain and how we treat pain is a very specific question.

I answered that question. I think there was

some evidence, too, or enough to support a yes vote, but I always say that with a little asterisk or a caveat that we do need to change how we are evaluating endpoints in terms of pain and looking at other solutions much farther beyond opioids in order to comprehensively treat pain and decrease addiction and abuse risk.

DR. CAMPOPIANO: Melinda Campopiano. I voted no, for basically the reasons I've already described.

DR. McCANN: Mary Ellen McCann. I voted yes, because I read the question very narrowly, but I do agree with Dr. Perrone that we should be using quality-of-life parameters to determine whether a drug is efficacious or not.

DR. EMALA: Charles Emala. I voted yes. I thought that data showed it had an acceptable improvement in pain scores over placebo.

DR. KAYE: Alan Kaye. I voted yes, for the reasons described. And I do hope, in the future, as Dr. Perrone mentioned, that we have the FDA define a higher bar or point so that we can get it

the best we can in the future. Thanks.

DR. PERRONE: Jeanmarie Perrone. I voted no, primarily because I'm really concerned about the number of very high-dose opioid drugs on the market. OxyContin was a high-dose all-in-one-pill drug and although it didn't have abuse-deterrent formulations when it first came out, it was that high dose that really got people problems with addiction and abuse.

This is another high-dose drug. It does have some abuse-deterrent formulation, but it's really the oral users who are still going to get as much as 90 milligrams in a dose, even in a patient who's taking it as prescribed by a physician, who may still feel euphoria associated with just a bigger dose at one time and that much of patients experiencing those drugs, experiencing those sensations are not in the expert drug abusers, but in the new initiates to opioids who may have a genetic predisposition or another predisposition to addiction that may occur in the exposure of very high doses, whether there's an abuse-deterrent

formulation or not.

DR. BROWN: This is Rae Brown. I voted yes.

DR. SHOBEN: Abby Shoben. I voted yes. I thought that their phase 3 study 3103 had met the standard for approval on the basis of pain reduction.

DR. MORRATO: Elaine Morrato. I voted yes. I also don't disagree with the concerns that were raised by Dr. Perrone. I voted yes, because I felt the clinical development program met the standards as specified by the FDA. There was pharmacokinetic evidence consistent with what you might expect with generic drug approvals, and it was augmented with the clinical efficacy safety data.

But having said that, I really do think it's important to FDA's efforts and the urgency of developing a better evidence base to guide long-term chronic use of opioids.

DR. CHOUDHRY: Niteesh Choudhry. I voted yes, as well, and I think I'm with perhaps the majority of the committee in the "yes, however" category. If there was another button, I'm sure

many of us would have picked that one instead.

Again, from the pure efficacy standard, I think it met the standard. There needs to be much more done in terms of figuring out outcomes for all of us.

DR. WALSH: I'm Sharon Walsh and I voted yes, because I think that the sponsor met the standard for demonstrating efficacy in this study as it was designed, and agree with the "however" that the outcomes should be revisited in future studies.

Then with respect to the changing landscape, because of your comment, Dr. Perrone, about the lower back pain, I would imagine that their phase 3 trial was completed well before those new recommendations came out from the CDC. And low back pain, despite its low yield in change scores in these problematic trials, has been one of the standard approaches.

DR. BESCO: Kelly Besco. I'm also a member of the "yes, however" camp. I definitely agree with the comments that have been made today about

our need to further understand the influence of outcomes based on multi-modal methods that are available today to manage pain.

I'm also concerned about the vast number of extended-release products available for potential abuse. But like others have said, I thought that the data presented today was consistent with efficacy of results available for similar products that have been FDA-approved.

DR. BATEMAN: Brian Bateman. I voted yes. I read this question narrowly, not as a referendum on chronic opioid use overall and the risks and benefits of that approach. But with respect to this agent, the data clearly meet the efficacy and safety standards.

DR. BROWN: For our next question, this is for a vote of the members of the committee. If approved, should Ventrela ER be labeled as an abuse-deterrent product by the oral route of abuse? Are there any further questions concerning this? We've already discussed this, to some extent, but if anyone has any further questions or comments,

we'd be pleased to entertain them now.

Dr. Choudhry?

DR. CHOUDHRY: I'm not sure, Dr. Brown, if you want this in commentary, but there's something about the label that we talked about earlier in the morning, Dr. Levin's presentation, the presentation of the information there and whether or not it's useful to providers.

At least as a comment, to the extent that we make a recommendation that this should indeed be the case, perhaps associated with that is the idea that the presentation of the information to providers actually be rethought.

I personally, despite the fact that I have a doctorate from Harvard and I'm a practicing physician, find some of the presentation actually pretty confusing. To that end, any recommendation we make about approving such a change in the label should be associated with the idea that we actually think about how those numbers are presented to prescribers and to patients.

DR. BROWN: I think this is exactly the

right time to discuss that. If you have any comments relating to that for the FDA, I'm sure they'd be pleased to get those now.

DR. CHOUDHRY: Sure, Dr. Brown. Thank you. For example, if I could just refer to Dr. Levin's talk, again, the proposed language -- and I appreciate comments from Dr. Hertz later that these are just potential suggestions. But what I found particularly difficult to understand -- or not difficult to understand, but potentially confusing, are Figure 2, which was on slide 9, and the analogous Figure 4, which is on slide 12 of Dr. Levin's presentation.

I obviously appreciate the intent here, but if this is the proportion of people receiving a given threshold, a percent reduction, but it takes quite a bit of time to figure out what this means, and it doesn't necessarily help me in terms of what I do for my individual patient. It tells me if I have a different risk tolerance threshold, what should I do, or perhaps if I have some vague assessment of my patient's potential for abuse,

what I might do. But it really doesn't provide a lot of guidance.

I think, in contrast, the tables, in this particular case, especially if we follow the logic of drug taking, take drug again kind of outcomes, with the Table 4 and analogous Table 5, which are on slides 8 and 11, respectively, at least from a transparency perspective, they are easier to follow.

We can make several arguments when communicating information. Some people like visual. Some people like tabular. But more is not always better. To the extent that some of this might be confusing and/or misleading, I'd at least rethink the graphical representation of what we're looking at.

DR. BROWN: Thank you. Dr. Morrato?

DR. MORRATO: Just to build on this -- this is Elaine. When you look at the graph, it implies that it's a larger population that may have been studied than it actually was. You're looking at an N of 34. Those percentages, people are going to be

naturally drawn to extrapolate to a population, and I think you run the risk of overinterpreting. But I agree with everything you just said, Dr. Choudhry.

DR. GERHARD: Toby Gerhard, Rutgers. In this same line, I think to make on the label clearer -- and I'm not a clinician, so I'm not sure to what extent that's perfectly clear to all practicing clinicians or patients, but I would think that it might not be.

I think it's important to maybe make explicit in the context of these abuse deterrence statements that abuse isn't a pre-condition to addiction.

You can get addicted to these drugs without actively abusing them or seeking to abuse them. In that sense, an abuse-deterrent formulation isn't necessarily a safeguard to addiction. And I think to make that clear might be something to be considered.

There are many people that know much more about this than I do, but I think it's important to

put it specifically in that same section when people read that information, that they don't get that wrong impression, because I think that's really the unintended consequence that we've been talking about a little bit.

DR. BROWN: I agree with you and in the past, we've heard other people say that in the following form, there is no safe dose of opiates.

Does anybody have any other questions or comments before we vote on this question number 3, which is, if approved, should Ventrela ER be labeled as an abuse-deterrent product by the oral route of abuse? Any other questions?

(No Response.)

DR. BROWN: If not, please press the button on your button that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

DR. BEGANSKY: The vote was 14 yes, 3 no, zero abstain.

DR. BROWN: Let's start this time with Dr. Bateman.

DR. BATEMAN: Brian Bateman. I voted yes, based on the data we've seen suggesting that Ventrela is resistant to high-yield extraction using the most common and straightforward methods that would be utilized by potential abusers.

We've also seen some reductions in PK and PD measures associated with oral use of the physically manipulated drug. And on that basis, I voted yes.

DR. BESCO: Kelly Besco. I also voted yes. I felt that the data provided today did establish that Ventrela has properties that one would expect to deter abuse, but I do want to acknowledge Dr. Gerhard's comments about while these products are abuse deterrent, addiction is still a possibility.

I believe that there are some warranted changes potentially to the labeling of these

products.

DR. WALSH: Sharon Walsh. And I voted yes, because I believe that both the in vitro and in vivo Category 3 data suggest that there's sufficient evidence for abuse deterrence by the oral route.

DR. CHOUDHRY: Niteesh Choudhry. I voted yes, for the reasons previously stated.

DR. MORRATO: Elaine Morrato. I voted yes, considering the totality of the evidence.

DR. SHOBEN: Abigail Shoben. I voted yes, for the reasons previously stated.

DR. BROWN: Rae Brown. I voted yes, for all the reasons previously stated.

DR. PERRONE: Jeanmarie Perrone. I voted yes.

DR. KAYE: Alan Kaye. I voted yes.

DR. EMALA: Charles Emala. I voted no, because of the Category 1 studies, where I'm skeptical that with an orally ingestible solvent that many abusers would have access to, the drug is easily extractible and ingestible.

DR. McCANN: Mary Ellen McCann. I voted no. I totally bought Dr. Emala's argument. I also think when you're dealing with oral medications, if one pill doesn't work, you just take two, you just take three. So I think the bar should be higher for oral deterrence.

DR. CAMPOPIANO: Melinda Campopiano. I voted yes.

DR. SPRINTZ: Michael Sprintz. I voted no, for the same reasons as Dr. Emala and Dr. McCann in regard to the Category 1 issues. I wasn't convinced that it actually would be of significance in a clinical practice.

DR. CHAUHAN: Cynthia Chauhan. I voted yes.

DR. HIGGINS: Jennifer Higgins. I voted yes.

DR. GERHARD: Toby Gerhard. I voted yes. I think the drug represents an incremental improvement regarding abuse deterrence.

DR. WESSELMANN: Ursula Wesselmann. I voted yes, for the reasons already stated.

DR. BROWN: We're going to move ahead to

question four. If approved, should Ventrela ER be labeled as an abuse-deterrent product by the nasal route of abuse? Any questions or comments? As I said before, we discussed this to some extent before, but if anyone has any other questions or concerns that they'd like to speak to now.

(No response.)

DR. BROWN: If not, please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or you want to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

DR. BEGANSKY: The vote was 14 yes, 3 no, and zero abstain.

DR. BROWN: We'll start on the other side this time.

DR. WESSELMANN: Ursula Wesselmann. I voted yes, because the data presented provide moderate

convincing evidence that this is an abuse-deterrent preparation and I see it as a step forward to make opioids safer that are needed for patients, for certain pain indications, and yet are not available necessarily or they deter others who want to abuse these drugs that are necessary for a certain patient population.

DR. GERHARD: Toby Gerhard. I voted yes. As before, I think it's a small incremental improvement.

DR. HIGGINS: Jennifer Higgins. I voted yes.

DR. CHAUHAN: Cynthia Chauhan. I voted yes, for the reasons stated.

DR. SPRINTZ: I'm Michael Sprintz. I voted yes, for those reasons. I think it was an incremental improvement.

DR. CAMPOPIANO: Melinda Campopiano. I voted no.

DR. McCANN: Mary Ellen McCann. I voted yes.

DR. EMALA: Charles Emala. I voted yes,

based on the viscosity results and, also, the likeability scores at early time points that I thought showed deterrence.

DR. KAYE: Alan Kaye. I voted yes, for the reasons mentioned.

DR. PERRONE: Jeanmarie Perrone. I voted no, because the Category 3 data about finely milled ground drug had very high liking, very comparable to the IR product.

DR. BROWN: Rae Brown. I voted yes.

DR. SHOBEN: Abby Shoben. I voted yes. This, I think, is a slight incremental improvement over the IR product and it remains to be seen how it would compare to the recently-approved abuse-deterrent product, but I understand that wasn't available at this time.

DR. MORRATO: Elaine Morrato. I voted yes, and I agree with the comments of Dr. Shoben.

DR. CHOUDHRY: Niteesh Choudhry. I voted yes. I also agree that there's some lack of clarity in the data or lack of consistency, although on balance, probably directs towards

greater safety. For me, the most compelling outcome was, again, this take drug again outcome, for which there is seeming superiority compared to the IR product.

DR. WALSH: Sharon Walsh. And I voted no, largely because of the very small margin of change in the direction of abuse deterrence in the Category 3 study, coupled with the large variability across subjects. And then I also thought that the in vitro data that used the nasal fluid, the promise of that wasn't borne out in the in vivo data.

DR. BESCO: Kelly Besco. I voted yes, for reasons that have already been stated.

DR. BATEMAN: Brian Bateman. I voted yes, for the reasons stated.

DR. BROWN: We're going to move on to question five now. If approved, should Ventrela ER be labeled as an abuse-deterrent product by the intravenous route of abuse? Are there any questions or comments about this? Again, we've had a little bit of discussion. If anyone has any

further discussion of Ventrela ER relating to the intravenous route of abuse, we'd be pleased to entertain those at this point.

(No response.)

DR. BROWN: Hearing none, please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

DR. BEGANSKY: The vote was 16 yes, 1 no, zero abstain.

DR. BROWN: Can we start with Dr. Bateman?

DR. BATEMAN: Brian Bateman. I voted yes, because of the data from the Category 1 studies showing the high viscosity of the drug and the challenge to syringeability.

DR. BESCO: Kelly Besco. I voted yes, for

the exact reasons stated by Dr. Bateman.

DR. WALSH: Sharon Walsh. And I voted yes, for the same reasons described before.

DR. CHOUDHRY: Niteesh Choudhry. I voted yes, for those same reasons.

DR. MORRATO: Elaine Morrato. I voted yes, for the same reasons.

DR. SHOBEN: Abigail Shoben. I voted yes.

DR. BROWN: Rae Brown. I voted yes.

DR. PERRONE: Jeanmarie Perrone. I voted yes.

DR. KAYE: Alan Kaye. I voted yes.

DR. EMALA: Charles Emala. I voted yes.

DR. McCANN: Mary Ellen McCann. I voted yes.

DR. CAMPOPIANO: Melinda Campopiano. I voted no, just because from experience with other viscous products, they do get injected and I don't have any basis to say that this is less injectable than those other viscous products getting injected. I'd have to say no.

DR. SPRINTZ: Michael Sprintz. I voted yes.

DR. CHAUHAN: Cynthia Chauhan. I voted yes.

DR. HIGGINS: Jennifer Higgins. I voted yes.

DR. GERHARD: Toby Gerhard. I voted yes.

DR. WESSELMANN: Ursula Wesselmann. I voted yes, but I also wanted to reemphasize what I said before, that I think that the post-marketing studies regarding the abuse deterrence are very, very important.

DR. BROWN: I'd like to thank the committee for their hard work today. I'd like to also thank the folks from Teva for concise presentations and being able to answer all of our questions.

Prior to adjournment, are there any last comments from the folks at FDA?

DR. HIGGINS: Thank you, Sharon. I just wanted to say that I really hope the post-marketing studies have much more representative populations, even older adults if possible, and have a greater number of measures used to evaluate functionality.

DR. HERTZ: I just want to say, also, thank you. You folks have gotten very efficient at this,

and I thank you. We're listening and look forward to tomorrow, and thank you.

**Adjournment**

DR. BEGANSKY: For the panel members who are coming back tomorrow, make sure you take everything with you from today. If you leave it here, it probably won't be here tomorrow.

(Whereupon, at 2:54 p.m., the open session was adjourned.)