FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE (AADPAC) AND THE DRUG AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

Wednesday, January 15, 2020

8:00 a.m. to 12:30 p.m.

Morning Session

FDA White Oak Campus

Building 31, the Great Room

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

(8:00 a.m.)

Call to Order

Introduction of Committee

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

Nathan, can you stand if you're here? Hi, Nathan.

I will now call the Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee to order. We will start by going around the table and introducing ourselves. We'll start with the FDA to my left and go around the table. Can you please -- this is for the panelists -- identify who you are and your expertise?

DR. STAFFA: Good morning. I'm Judy Staffa. I'm the associate director for Public Health Initiatives in the Office of Surveillance and Epidemiology in the Center for Drugs.

DR. ROCA: Good morning. My name is Rigo Roca. I'm the acting director for the Division of Anesthesiology, Addiction Medicine, and Pain Medicine.

DR. LOWY: Good morning. I'm Naomi Lowy. I am the acting deputy director for the Division of Anesthesiology, Addiction Medicine, and Pain Medicine.

DR. HORN: Hi. I'm Pamela Horn. I'm a clinical team leader in the same division.

DR. CHIAPPERINO: Good morning. I'm Dominic Chiapperino. I'm director of the controlled substance staff in CDER.

MS. SHAW PHILLIPS: Good morning. Marjorie Shaw Phillips, clinical research pharmacy coordinator at AU Medical Center, Augusta University, and clinical professor at University of Georgia College of Pharmacy, med-use safety.

DR. GARCIA-BUNUEL: Good morning. Martin Garcia-Bunuel. I'm a primary care physician and the deputy to the staff for the VA Maryland Health Care System.

DR. GREEN: Traci Green. I'm an epidemiologist and the professor and director at the Opioid Policy Research Collaborative at The Heller School at Brandeis.

DR. HOFFER: Lee Hoffer. I'm an associate professor of medical anthropology and psychiatry at Case Western Reserve University in Cleveland, Ohio.

DR. MICHNA: Ed Michna, anesthesia and pain physician, Brigham and Women's Hospital in Boston.

DR. SETOGUCHI: Soko Setoguchi. I'm a general internist and pharmacoepidemiologist at Robert Wood Johnson Medical School.

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

DR. ZACHAROFF: Good morning. Kevin Zacharoff. My expertise is in anesthesiology and

pain medicine. I am a faculty clinical instructor and course director of pain and addiction at the Stony Brook School of Medicine.

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

DR. ZELTZER: Hi. I'm Lonnie Zeltzer. I'm distinguished professor of pediatrics, anesthesiology, and psychiatry at University of California Los Angeles and head of the Pediatric Pain and Palliative Care Program.

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

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

DR. LITMAN: Good morning. Ron Litman. I'm a professor of anesthesiology and pediatrics at Penn School of Medicine, Children's Hospital, Philadelphia and the medical director of the Institute for Safe Medication Practices.

DR. HERNANDEZ-DIAZ: Good morning. Sonia Hernandez-Diaz, professor of epidemiology at the Harvard Chan School of Public Health in Boston.

DR. SHOBEN: I'm Abby Shoben. I'm a biostatistician at
The Ohio State University.

DR. MEISEL: Steve Meisel, director of medication safety for M Health Fairview in Minneapolis.

DR. HIGGINS: Jennifer Higgins, the consumer representative to AADPAC.

MS. ROBOTTI: Suzanne Robotti, executive director of MedShadow Foundation and executive director of DES Action USA.

DR. BLOCK: Laura Block. I'm a pharmacist and a partner in Usagi Medical Group.

DR. AMIRSHAHI: Maryann Amirshahi. I'm an emergency medicine physician, medical toxicologist and addiction medicine physician here in Washington, D.C., affiliated with MedStar and Georgetown University.

DR. PISARIK: Paul Pisarik, urgent care

physician, Saint Francis Health System, Tulsa, Oklahoma.

DR. SANDBRINK: I'm Friedhelm Sandbrink. I'm a clinical associate professor of neurology at Uniformed Services University in Bethesda. I lead the pain program at the Washington, D.C. VA Medical Center, and I'm the national program director for pain management for the Veterans Health Administration.

DR. ZAAFRAN: Sherif Zaafran, anesthesiologist, Houston, Texas, Memorial Hermann Healthcare System, Chronic and Acute Pain Care Committee; vice chair of Clinical Governance Board for US Anesthesia Partners Gulf Coast.

DR. SUAREZ-ALMAZOR: Good morning. Maria Suarez-Almazor. I'm a rheumatologist and clinical epidemiologist and professor at the University of Texas MD Anderson Cancer Center.

DR. SULLIVAN: Good morning. I'm Patrick Sullivan. I'm an infectious disease epidemiologist at Emory University in Atlanta.

DR. MARSHALL: Good morning, everyone. I'm

Brandon Marshall. I'm an associate professor in epidemiology at the Brown University School of Public Health in Providence, Rhode Island.

DR. TYLER: Good morning. I'm Linda Tyler. I'm the chief pharmacy officer for University of Utah Health and associate dean in the College of Pharmacy.

DR. MEHTA: Hi. Good morning. Reema Mehta from Pfizer, head of Risk Management and Safety Surveillance Research.

DR. HORROW: My name is Jay Horrow. I'm the industry representative to the AADPAC and anesthesiologist. I'm clinical trial lead in cardiovascular medicines at Bristol-Myers Squibb.

DR. LITMAN: Thanks, everybody.

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

individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

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

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

Now, I'll pass it on to Moon Hee Choi who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's 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 representatives, all members and temporary voting members of the 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 this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants 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 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.

The morning session of today's agenda involves discussion of new drug application, NDA 213426, for tramadol 44 milligrams and celecoxib 56-milligram tablet, which contains a

fixed-dose combination of an opioid and a nonsteroid anti-inflammatory drug submitted by Esteve Pharmaceuticals for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The committees will be asked to discuss the safety and efficacy data as well as the overall risk-benefit profile of the product.

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

With respect to FDA's invited industry representatives, we would like to disclose that

Drs. Jay Horrow and Reema Mehta are participating in this meeting as nonvoting industry representatives, acting on behalf of regulated industry. Drs. Horrow's and Mehta's role at this meeting is to represent industry in general and not any particular company. Dr. Horrow is employed by Bristol-Myers Squibb and Dr. Mehta is employed by Pfizer.

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

DR. LITMAN: Thanks, Moon.

We will now proceed with the FDA's introductory remarks from Dr. Naomi Lowy.

FDA Opening Remarks - Naomi Lowy

DR. LOWY: Good morning. Welcome to the advisory committee, the applicant and members of the public, to today's meeting. During this half-day session, we will be discussing Esteve's new drug application for celecoxib-tramadol, a fixed-dose combination drug product.

The proposed indication is for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The applicant has developed a formulation of two analgesics of different classes such that the proposed recommended dose of each component of the drug is less than the recommended dose of each component when taken individually for the management of acute pain. The product contains tramadol, an opioid with abuse potential, and the product has not been formulated in a manner intended to impart abuse-deterrent characteristics.

The company's phase 3 factorial study provides evidence that the combination product

provides analgesic efficacy. In addition, our review of the safety data from this program did not reveal any novel risks for the two drugs in the combination. The Comprehensive Addiction and Recovery Act of 2016, Section 106, requires that FDA refer new drug applications for opioids to an advisory committee before approval.

The company will begin this morning's presentations. Although FDA will not be presenting standard efficacy and safety data beyond those included in your background document, you will hear one presentation from FDA in which Dr. Wittayanukorn, our epidemiologist, will review recent data on use, misuse, and abuse of tramadol and comparator drugs. We hope that these data inform your thinking of this product's risk-benefit assessment in the current landscape.

After clarifying questions, a break, and the open public hearing, I will then give the charge to the committee. As you listen this morning to the presentations and clarifying questions, please keep in mind we will be asking you to discuss two

points. I will not go through them in detail, but the first point asks you to think about the abuse potential of this product and its impact on public health. The second point asks you to weigh benefit-risk and if any additional data are needed. And finally, you will be asked to vote on whether you recommend approval.

Thank you again for your participation, and we look forward to an informative discussion.

DR. LITMAN: Thanks, Dr. Lowy.

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

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant such as consulting fees, travel

expenses, honoraria, and interest in the sponsor, including equity interests and those based on the outcome of the meeting.

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

We will now proceed with Esteve Pharmaceutical's presentation.

Applicant Presentation - Mark Mayhew

DR. MAYHEW: Good morning. My name is Mark Mayhew, and I'm the director of the CTC Program at Esteve. I want to start by thanking the FDA and the advisory committee members for the time you've spent preparing for today's meeting.

As we all know, there is an urgent need for analgesic medications that can provide substantial efficacy with a low potential for abuse and dependence. We believe that our co-crystal is such

a medication. As we will show you today, CTC significantly improves upon the efficacy of tramadol, a Schedule IV opioid, to create a viable alternative to Schedule II opioids for appropriate patients.

I would like to provide the rationale for creating a co-crystal rather than a simple fixed-dose combination. A simple fixed-dose combination combines two active pharmaceutical ingredients, or APIs, into one dosage form. Such combinations retain the same dissolution profiles and the same PK as either of the APIs taken alone, with the goal of providing improved efficacy over either drug; however, the pharmacology of each API remains the same.

A co-crystal is different because the components are bonded in a crystalline structure. Unlike standard fixed-dose combination, the intention is to create different dissolution profiles for both APIs, which translates into differentiated pharmacokinetics. The clinical goal is to improve efficacy and safety or tolerability

over each API taken alone or taken together.

The discovery of a therapeutically useful co-crystal is a complex process. In the drug discovery phase, we sought a compound that met four specific criteria. First, the APIs had to act on complementary mechanisms and sites of action; second, they had to provide pain relief and anti-inflammatory properties; third, they had to have physicochemical properties and pharmacokinetic characteristics that could be improved; fourth, there had to be no known deleterious interactions between them.

The ability to co-crystallize to APIs is difficult to predict because it depends on the chemical structures of the individual components, therefore, we applied the technology to many potential pairs. Once such a co-crystal is generated, the molecular ratio between the two APIs has to be clinically relevant and therapeutically useful. Lastly, the co-crystal needs to modify the profiles of both components in a favorable manner to improve the clinical characteristics compared

with both APIs taken alone or together.

In Esteve's experience, the probability of creating a co-crystal meeting all criteria for clinical utility is very low, less than 0.01 percent. CTC is a first-in-class API and API co-crystal of two FDA-approved analgesics, tramadol and celecoxib. The novel co-crystal structure provides a differentiated and improved pharmacology of both APIs in a multimodal treatment approach. For the presentation today, we will be referring to the co-crystal as CTC, which stands for the co-crystal of tramadol and celecoxib. This is the name we have used to refer to the product in scientific literature. We've also used the code E-58425.

CTC is a new chemical structure in which tramadol and celecoxib are integrated in a defined one-to-one, stoichiometric ratio within the same crystal lattice through non-covalent hydrogen bonds. CTC is formulated as a 100-milligrams immediate-release tablet. Each tablet contains 44 milligrams of tramadol and 56 milligrams of

celecoxib. The ratio of tramadol to celecoxib is defined by the crystallization process. The dosing regimen is 2 tablets every 12 hours.

Like all opioids, CTC should be used for the shortest duration consistent with individual patient treatment goals. Based on the results of a food effect study, CTC can be administered without regard to meals. Since tramadol is rarely abused by nonoral routes, CTC was not formulated with abuse-deterrent excipients.

One of the most important considerations in the benefit-risk profile of an opioid analgesic is its abuse potential. The DEA schedules drugs in consultation with the FDA based on whether they have an accepted medical use and their inherent potential for abuse and dependence.

Schedule I drugs such as heroin have high abuse potential and do not have an acceptable medical use. Schedule II drugs also have a high abuse potential but do have an acceptable medical use. These include opioids such as oxycodone and hydrocodone. Schedule IV drugs have a low

potential for abuse and a low risk of dependence. CTC contains tramadol, which is an opioid in this category. The other component, celecoxib, has no abuse potential.

CTC targets for complementary pain relief mechanisms in a multimodal treatment approach. Tramadol and its active metabolite reduce pain as a partial agonist of the mu-opioid receptor and by inhibiting the reuptake of serotonin and norepinephrine. Celecoxib is a nonsteroidal anti-inflammatory drug that selectively inhibits COX-2, an enzyme responsible for inflammation and pain. These analgesic and anti-inflammatory properties are complementary and synergistic, improving the ability to modulate the perception of and response to pain.

Tramadol and celecoxib are both FDA-approved products and have been used in clinical practice for more than 20 years. Immediate-release tramadol was approved by the FDA in 1995. For acute pain, tramadol is administered at 50 to 100 milligrams as needed every 4 to 6 hours with a maximum daily dose

of 400 milligrams in adults. The maximum daily dose is reduced in special populations; 200 milligrams per day in patients with impaired creatinine clearance and 300 milligrams per day for patients 75 and older.

The daily dose of CTC contains 176 milligrams of tramadol, less than half of the approved maximum for tramadol alone in adults, and is also below the maximum dose in special populations.

Celecoxib was first approved by the FDA in 1998 for the treatment of osteoarthritis and rheumatoid arthritis. It was approved for the treatment of acute pain in adults in 2001. For acute pain, the initial dose is 400 milligrams and 200 milligrams twice daily thereafter. The maximum daily dose for adults is 600 milligrams on the first day and 400 milligrams thereafter.

In patients with moderate hepatic impairment, the celecoxib label recommends reducing the dose by approximately 50 percent. The daily dose of CTC contains 224 milligrams of celecoxib,

which is about half of the approved maximum for celecoxib alone in adults.

Given the extensive existing data with both of its FDA approved APIs, the new drug application for CTC was filed under the 505(b)(2) regulatory pathway. This allows the agency to rely on the previous findings of safety and effectiveness for the reference-listed drugs, Ultram and Celebrex. The agency determined that one full factorial phase 3 study would be sufficient to support the NDA. By full factorial design, we mean that CTC had to demonstrate significantly greater efficacy than its individual APIs at comparable doses as present in CTC.

The CTC new drug application is supported by five phase 1 studies, one phase 2 study, and one phase 3 study. Today we will focus on the results from our pivotal single-dose and multiple-dose crossover studies, our phase 2 dose-finding study, and our pivotal phase 3 trial. Results from our clinical development program demonstrate CTC's positive benefit-risk profile.

As we will show today, the co-crystal provides a favorable and differentiated pharmacology of both its active ingredients. This translates into greater efficacy than both of its individual APIs, as well as better tolerability and a comparable overall safety profile relative to tramadol.

Importantly, CTC has a low potential for abuse and a low risk of dependence consistent with tramadol's Schedule IV classification. These data suggest that CTC will be a favorable treatment alternative for appropriate patients with acute pain who might otherwise be prescribed a Schedule II opioid. In this way, CTC may reduce exposure of patients and communities to opioid medications that have a higher potential for abuse and dependence.

We are requesting the same indication as currently approved for tramadol; that is for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Here is the agenda for the remainder of our

presentation. We also have additional experts with us today, including Dr. Rick Dart from the RADARS system. All experts or their institutions have been compensated for their time and travel to today's meeting. None have an equity interest in today's outcome. Thank you, and I'll now pass the lectern over to Dr. Viscusi.

Applicant Presentation - Eugene Viscusi

DR. VISCUSI: Thank you and good morning. I am Gene Viscusi. I'm a professor of anesthesiology and chief of pain medicine at Thomas Jefferson University in Philadelphia. I'm also the current president of ASRA, the American Society of Regional Anesthesia and Pain Medicine.

I am incredibly proud of ASRA's more than 45 years supporting non-opioids, minimizing opioids, and promoting regional anesthesia techniques for perioperative pain management. I've dedicated much of my career in academic medicine to the research and development of newer and safer treatments to reduce reliance on opioids, to advance multimodal analgesia, and to develop guidelines for the

treatment of postoperative pain.

We are caught in a dilemma. We all acknowledge the opioid crisis and we all work to reduce the amount of opioids available in the public availability, but we also have an obligation to treat pain. For those patients whose pain is severe enough to warrant an opioid, in addition to multimodal techniques, there is an urgent need for treatment options that have efficacy with a lower potential for abuse and dependence.

Professional societies have developed comprehensive evidence-based guidelines for postoperative pain management. The heart of these programs is virtually always the advancement of multimodal analgesic techniques. That concept is the use of a variety of analgesic medications and regional anesthesia techniques in combination to reduce postoperative pain.

I have been at times accused of promoting picking patients with multiple drugs, and it's very important to understand that multimodal analgesia is not just throwing a bunch of analgesics at

patients; it recognizes that pain, postoperative pain, has multiple pathways and is a mixed-pain syndrome.

The concept of multimodal analgesia is targeted analgesic therapy, understanding those pathways so that you can get the most pristine, comprehensive approach to all of those drivers for pain for particular kind of exposure; then by doing so, you can minimize opioids where they are used as adjunctive agents. So the concept is now we can minimize opioids and non-opioid medications to the lowest doses to produce the safest and best analgesia.

The misuse, abuse, and dependence of prescription opioids remains a serious public health crisis. Use of perioperative opioids can lead to chronic opioid use. A recent paper by Chad Brummett published in JAMA Surgery demonstrated that between 6 and 10 percent of patients who have had surgery and received an opioid will still be using opioids in a year. That translates to 2 million patients a year with persistent opioid

use. Therefore, our best practices for perioperative pain management are to rely on non-opioid, multimodal analgesic techniques, regional anesthetic techniques with local anesthetics, and the lowest opioid dose for the shortest period of time.

Much of the concern around the abuse of prescription opioids is with respect to the Schedule II opioids which have the highest rate of abuse. Data from the U.S. conducted by the RADARS system shows that tramadol is associated with a low rate of abuse. Most abuse of opioid medications is by the oral route. Tramadol is associated with less than half of the rate of oral abuse relative to oxycodone and hydrocodone. In terms of the more dangerous nonoral routes such as inhalation and injection, the abuse of tramadol is low.

Another way to evaluate relative potential for abuse is to simply ask individuals who abuse opioids which they prefer. This is exactly what the researchers at Washington University in St. Louis did. They surveyed 738 opioid-dependent

individuals and asked them to rank order their preferred opioids. The survey found that oxycodone and hydrocodone had the highest preference; tramadol was last on this list. This is consistent with the DEA schedules of the various types of opioids. The reason for the low preference of tramadol is because it is simply hard to get high with tramadol.

On this slide, I will show results of a human abuse potential study that evaluated various doses of oral tramadol. On the Y-axis, I show the drug-high results on a 100-point VAS unipolar scale; zero is not high at all and 100 hundred means extremely high. I'll plot the maximum or Emax scores.

As expected, placebo doesn't produce a high. The 87.5-milligram tramadol dose didn't separate from placebo. This is notable since 88 milligrams of tramadol is what is contained in a single therapeutic dose of CTC. Even the supratherapeutic doses of tramadol at 175 and 350 milligrams, which would be the equivalent of 2 and 4 times the dose

of CTC, did not lead to meaningful endorsement of drug high.

For comparison, here are the drug-high results for oral hydrocodone and oxycodone. The drug-high results for tramadol were lower than the supratherapeutic doses of both immediate-release hydrocodone and oxycodone products. These were evaluated in other human abuse studies that used the same VAS score. Similar results were seen for drug liking.

To summarize, historically, opioids have been used as stand-alone agents for postoperative pain. This has unquestionably contributed to the opioid crisis; major adverse events such as respiratory depression and nuisance opioid side effects; and persistent use, abuse, and misuse.

Today, multimodal analgesia should be considered standard care for postoperative pain and should rely first on that foundation of non-opioid analgesics and whenever possible, regional anesthetic techniques and local anesthetic techniques. For appropriate patients, opioid

analgesics still have a useful place as adjuncts in multimodal analgesia.

We have treated the Schedule II opioids as the gold standard for postoperative pain, and what I can say from my experience with these drugs is that we have given them credit for analgesic potency that they just don't have, and this has given us this incredible lead into the current opioid crisis. There is an inherently high potential for abuse and dependence with these agents.

Tramadol has less abuse liability than Schedule IV opioids, but as a stand-alone agent, it has been perceived as being less effective than Schedule II opioids. However, in the context of contemporary multimodal analgesic techniques, tramadol is an effective analgesic agent.

The message I want to leave you with is that the treatment of postoperative pain remains a significant healthcare need. The past history of reliance on Schedule II opioids as stand-alone agents has resulted in a contribution to the opioid

crisis and the chronicity of opioid use. It is inappropriate to use opioids alone in the context of contemporary multimodal analgesia. We need opioid alternatives with low-abuse liability than the Schedule II products.

Thank you, and now I'll turn over the presentation to Dr. Plata-Salaman.

Applicant Presentation - Carlos Plata-Salaman

DR. PLATA-SALAMAN: Good morning. I am Carlos Plata-Salaman, chief scientific officer and chief medical officer at Esteve. I am pleased to present the phase 1 clinical pharmacology data and the results from our phase 2 dose-finding study.

Phase 1 single- and multiple- dose crossover studies provide a clear assessment of pharmacokinetics, safety, and tolerability. Crossover designs provide certain distinct advantages over parallel group designs. Since all participants receive each of the study drugs in a random order, they act as their own control, which addresses genetic and metabolic heterogenicity. The design also avoids confounding the safety and

tolerability profile from rescue and concomitant medication that cannot be done in a phase 3 trial in acute pain. Therefore, crossover designs provide precise estimates of the effects of each study drug.

In the case of CTC, these studies support the difference of co-crystal effect compared to the individual components and the combination, and contribute to the understanding of the totality of the clinical profile of CTC.

I will now start the presentation of results with Study 101. This was a single-center, randomized, single-dose, open-label, 4-way crossover bioavailability study in 36 healthy volunteers under fasted conditions. The study evaluated the PK profile of CTC compared to tramadol alone, celecoxib alone, or tramadol and celecoxib taken together.

Here tramadol refers to Ultram and celecoxib to Celebrex. Participants received only study drugs in a random order with a 7-day washout period between each dose. First, let us look at the

tramadol plasma concentration curves over the first 12 hours, the proposed dosing interval for CTC.

This is the tramadol PK curve for tramadol alone. The tramadol PK curve for tramadol administered with celecoxib was essentially identical. The tramadol PK curve for CTC is plotted in blue. Compared to tramadol alone or with celecoxib, CTC has a lower Cmax and a later Tmax. Similar results were observed for tramadol's active metabolite M1. With CTC, this lower onset of tramadol and its metabolite provided a better tolerability profile than tramadol taken alone or with celecoxib.

One of the primary issues with opioids are patients' intolerance to gastrointestinal adverse effects such as nausea and vomiting. The incidence of opioid-related adverse events with CTC was 3 percent compared to approximately 20 percent for both tramadol alone or with celecoxib, showing the co-crystal effect. These differences in tramadol PK intolerability show that the co-crystal is different than a simple combination product.

Next, let us look at celecoxib. Here is a PK curve for celecoxib taken alone. Next, as you can see, celecoxib absorption is inhibitive when co-administered with tramadol in a simple combination. The celecoxib PK curve for CTC is plotted in blue. CTC eliminates the interference of celecoxib absorption when taken with tramadol and also accelerates absorption relative to celecoxib taken alone.

The favorable PK profile of CTC was replicated in a multiple-dose crossover study in healthy subjects who received the study drugs in a random order with 12-hour dosing over a 7 and a half day period. We confirmed the favorable tramadol and celecoxib PK absorption with multiple-dose administration, including the lower and longer Cmax for tramadol and M1, one faster absorption of celecoxib, and the lack of interference with celecoxib absorption when administered with tramadol.

We also replicated the favorable tolerability findings. The incidence of overall

adverse events and related adverse events with CTC were half that of tramadol and were lower than the co-administration of tramadol and celecoxib as well. Full results for this study were provided in our briefing book.

To summarize, results demonstrate that CTC improves the pharmacologic profile of its APIs compared to the individual or combined administration. CTC provides a lower Cmax or peak concentration and a longer Tmax for tramadol, as well as faster absorption of celecoxib. These features were shown to provide better tolerability for tramadol in terms of opioid-related adverse events. We would expect an efficacy benefit for faster absorption of celecoxib as well.

CTC also eliminates the interference in celecoxib absorption that occurs with tramadol when administered as a simple combination. This shows that CTC is structurally and pharmacologically distinct from a simple combination, supporting the benefits of its co-crystal extraction. Data from our phase 1 studies demonstrate similar results in

female and male subjects with single and multiple doses of CTC twice daily for 7 days in fed and fasted conditions in subjects with different ethnicities and in studies in the United States and out of the United States.

Next, I will review the results from our phase 2 dose-finding Study 201. Its goal was to identify a dose of CTC that would provide maximum efficacy without increasing the incidence of adverse events relative to tramadol alone. First, I will review the primary efficacy endpoint, the sum of pain intensity differences, or SPID, from 0 to 8 hours.

This slide will show the primary endpoint results. A score less than zero represents a reduction in pain intensity. In the four CTC dose groups, we observed a dose-dependent effect as would be expected with an analgesic. In contrast, pain scores increase slightly through 8 hours in the tramadol and placebo groups.

All CTC doses, except the lowest dose, showed statistically significantly better pain

control than placebo and tramadol, with CTC 200 milligrams providing the greatest reduction in pain scores from 0 to 8 hours. One of our secondary endpoints was SPID from 0 to 12 hours. Similar results were observed for SPID from 0 to 12 hours, as was observed for the primary endpoint through 8 hours. These results suggested that 12 hours was a suitable dosing interval for CTC.

Next, I will review the safety results from Study 201. As would be expected for an analgesic, the incidence of adverse events increase with higher CTC doses. The rate of adverse events with CTC 200 milligrams was similar to tramadol 100 milligrams, which were mostly opioid related. These align with the study goal of identifying the CTC dose that maximizes efficacy without potentiating adverse events relative to tramadol. There were no adverse events that led to treatment discontinuation in any group.

In summary, results from our phase 2 study demonstrated that CTC 200 milligrams provided maximum analgesic efficacy while maintaining a

comparable safety profile to tramadol alone. In addition, sufficient pain relief was demonstrated with 12-hour dosing. Based on these conclusions, we move forward with CTC 200 milligrams every 12 hours for the phase 3 study.

Thank you. I will now turn the presentation over to Dr. Gascon.

Applicant Presentation - Neus Gascon

DR. GASCON: Thank you. I am Neus Gascon, head of medical sciences, and I will present the phase 3 efficacy and safety data, starting with the design and efficacy results from our pivotal Study 301. This was a randomized, double-blind placebo and active-controlled study in bunionectomy with osteotomy. This is a common surgical pain model for new analgesics because it is an intensely painful bun removal procedure that typically requires opioids to manage pain.

1,323 patients were screened for Study 301. Prior to surgery, patients received regional anesthesia via continuous popliteal sciatic nerve block. Unlike clinical practice, the morning after

surgery, patients had the nerve block discontinued, and their pain scores were evaluated. Only patients who reached a moderate to severe pain score were randomized. Overall, 637 patients were randomized to receive CTC, tramadol, celecoxib, or placebo.

This clinical trial was designed based on advice from the FDA. The FDA recommended a full factorial study to demonstrate a significant improvement of CTC versus each of the individual active components and a placebo group to support assay sensitivity. Study medication, either an active drug or placebo, was administered every 6 hours for 48 hours. This double-dosing schedule was used to blinding of the study participants to the treatment they received.

The dosing for the tramadol and celecoxib arms was based on FDA recommendations. CTC was administered at the total daily dose of 400 milligrams, which contains 176 milligrams of tramadol and 224 milligrams of celecoxib. The total daily dose of tramadol and celecoxib were

both 200 milligrams.

The primary efficacy endpoint was the sum of pain intensity differences from 0 to 48 hours. Pain was measured at many time points throughout the study using a numeric pain rating scale, where zero represents no pain and 10 represents the worst possible pain. Pain scores were adjusted for the use of rescue medication. This information can be found in our briefing document.

Baseline characteristics were similar between the groups. The mean age was approximately 46 years and ranged from 18 years to 77 years. The majority of patients were female and approximately 20 percent of patients were African American. The mean BMI was approximately 28. The rate of treatment discontinuations or study withdrawals were consistent, low across all the treatment groups, supporting that CTC is well tolerated.

Before moving to the study results, I want to briefly discuss the ways in which efficacy is characterized. Endpoints relating to the magnitude of efficacy are the primary endpoints in trials for

regulatory approval. These endpoints evaluate pain scores at different time points and cumulative pain relief such as SPID. However, we cannot only use measures of magnitude since you can always get lower pain scores by just increasing the dose of an opioid. This is why we also look at sufficiency of efficacy, the ability to provide clinically meaningful pain relief with the lowest exposure to rescue medication.

Let's review the results starting with the endpoints related to the magnitude of efficacy. On the primary efficacy endpoint, CTC demonstrated a statistically significantly lower pain score than tramadol, celecoxib, and placebo through 48 hours, so the primary efficacy endpoint was met. Since treatments for pain have a substantial placebo effect, the magnitude of efficacy needs to be compared after adjusting for the effect of placebo.

This forest plot illustrates the placebo-adjusted treatment effect for CTC, tramadol, and celecoxib. Scores to the left of zero indicate greater efficacy than placebo, and as

you can see, CTC approximately doubled the analgesic efficacy of each of its individual components, showing that the differences between CTC and its active components were not only statistically significant but also clinically relevant.

This slide will show the average change from baseline in pain scores over the 48-hour treatment period with imputation for rescue medication use. The table in the upper right shows the daily dosing schedule. The baseline mean pain intensity score for all the treatment groups was 6.7. Decreasing pain score over time was observed in the placebo group. Tramadol and celecoxib, shown in red and pink, provided reductions in pain compared with placebo; and now including CTC in blue, pain scores separated early and were lower than all the other groups at every time point.

Next, let's review the sufficiency of efficacy, which we assess by comparing the use of rescue medication. First-line rescue medication was intravenous acetaminophen, which was used by

most patients in all treatment groups, however, the most relevant public health measure for rescue is the use of Schedule II oxycodone. The lower use of oxycodone rescue in the CTC group was evident a few hours after the first dose and was sustained throughout the 48 hours. Through 48 hours, fewer patients in the CTC group had requested oxycodone rescue medication.

We also evaluated the use of rescue medication over time to evaluate the sufficiency of the proposed 12-hour dosing interval for CTC. This slide will show the percentage of CTC patients using oxycodone rescue on the Y-axis relative to different time intervals on the X-axis. As you can see, the percentage of patients utilizing oxycodone rescue over time was low in each interval.

These arrows identify the timing at each CTC dose over the 48-hour treatment period. There was no sign of a clinically significant increase in the need for oxycodone rescue at the 12-hour dosing time points, suggesting that the proposed 12-hour interval for CTC is appropriate.

Next, I will review the CTC tolerability and safety profile. Consistent with our prior studies, CTC was associated with better tolerability relative to tramadol alone. In the 2 hours after the first dose, even though CTC patients received nearly twice as much tramadol as the tramadol-alone group, 88 versus 50 milligrams, the rate of overall adverse events and opioid-related adverse events was lower with CTC.

This finding is particularly relevant since 50 milligrams is the lowest dose of tramadol used for acute pain. The favorable tolerability profile of CTC relative to tramadol alone further supports the clinical benefits of the co-crystal in patients.

This slide summarizes safety from enrollment to about 9 days after surgery, including the aggregate of adverse events from study drugs, concomitant and rescue medications, and medical procedures. Most patients in all treatment groups experienced an adverse event. Adverse events related to study drug were 38 percent for CTC and

49 percent for tramadol. The majority of adverse events were mild to moderate in intensity, and no patients experienced a serious adverse event.

The rates of adverse events leading to discontinuation of study medication were low. The most common adverse events in all groups were of gastrointestinal nature, including nausea, vomiting, and constipation. Compared to tramadol, CTC was associated with similar or fewer gastrointestinal adverse events, however, the rate was higher compared to celecoxib and placebo, as would be expected with an opioid.

In summary, the development program has demonstrated the clinical benefits of CTC. Its differentiated pharmacology and multimodal approach provides greater magnitude and sufficiency of efficacy than its components with a better tolerability and comparable safety profile to tramadol. CTC provides patients with significant relief from acute pain with an intrinsically low abuse potential.

Thank you for your attention, and I will now

turn the presentation to Dr. de Leon to provide his benefit-risk assessment of CTC.

Applicant Presentation - Oscar de Leon-Casasola

DR. DE LEON-CASASOLA: Thank you so very much. Good morning to all the members of the committee. I am Oscar de Leon-Casasola. I am the chief of the Division of Pain Medicine at the Roswell Park Cancer Institute and professor of oncology there. I'm also a professor of anesthesiology and medicine at the university at Buffalo School of Medicine.

From 2015 to 2017, I had the honor to serve as the president of the American Society of Regional Anesthesia and Pain Medicine. Dr. Viscusi outlined the goals of the society and the achievements in the space of acute pain medicine.

I was also fortunate to co-chair the Joint Committee of the American Society of Anesthesiologists; the American Society of Regional Anesthesia and Pain Medicine; and the American Pain Society, which drafted the guidelines for treatment of acute pain that were published in 2016. Esteve

requested my participation today to provide a benefit-risk assessment of CTC. Dr. Mayhew has already established my conflicts of interest with the company.

As you are aware, in June of 2019, the FDA issued a draft framework to guide the benefit-risk assessment of novel opioid analgesics. This guidance recognizes that opioids are essential medications, though they pose unique risks to patients and public health that require careful consideration.

I will be using the five FDA domains in this framework to guide my assessment. The first domain us benefits to patients. The data presented today, along with decades of both tramadol and celecoxib abuse that have allowed a lot of assessments as far as efficacy in this space, showed that CTC will be an effective analgesic for acute pain treatment.

In the phase 3 trial, CTC showed greater efficacy than tramadol or celecoxib, suggesting that it will be a favorable treatment alternative to Schedule II opioids for an appropriate group of

patients. Since CTC contains an equivalent low opioid dose, the expectation is that it will provide important safety advantages as well. Please allow me to explain this statement.

The slide shown here has the maximum daily opioid doses for Percocet, Vicodin, Ultram, and CTC. To compare relative opioid risk, that is to say compare apples to apples, we need to convert the maximum daily dose into morphine milligram equivalents or MME. Here I am using the conversion factors published by CMS.

When we multiply the maximum daily dose by the conversion factor, we get the maximum daily dose in MME, 90 for Percocet, 60 Vicodin, 40 for Ultram, and 17.6 for CTC. This is very important because MME add an important value since there is a strong relationship between the amount of opioid exposure and mortality risk from respiratory depression.

This figure shows the results from a large case control study of more than 600,000 patients carried in the province of Ontario in Canada. The

odds ratios show the likelihood of drug-related mortality due to respiratory depression for different ranges of daily doses of opioids compared to a low daily dose of 20 MME or less. This is the dose that corresponds to the daily opioid dose in CTC.

The mortality risk, as you can see, was 2 to 3 times higher for patients receiving opioid doses greater than 50 MME when they compared to those who received less than 20 MME per day. There was a modest signal of increased risk for doses above 20 MME as well; hence, the recommendations from the surgeon general for the observation of these patients when they are getting doses greater than 50 MME.

Based on this study and others, the CDC has provided guidelines to clinicians for safer opioid prescribing. The CDC considers doses of 20 to 50 MME per day as relatively low and doses above 50 MME per day as high. The maximum daily dose of Percocet and Vicodin will fall into the high range. Ultram will be in the relatively low range.

Conversely, the daily dose of CTC is below the threshold and is considered a low opioid dose.

Regarding risk to patients, no safety risk beyond those known for tramadol or celecoxib were observed in the clinical program. Moreover, all excipients in CTC are generally regarded as safe by the FDA and have not been linked to unusual health risks or unintended consequences. Additionally, as shown in the large cardiovascular outcomes trial, the PRECISION trial, celecoxib is not associated with increased risks relative to ibuprofen or naproxen.

The third benefit-risk domain is the effectiveness and safety of the new drug relative to approved analgesics. We have already discussed that CTC provided greater efficacy than its individual APIs. A review of the literature provides further insight.

The sponsor conducted a systematic review to identify studies of Schedule II opioids that were similar in design to their own phase 3 study. This was done to ensure that reasonable comparisons

could be made. The review was restricted to randomized trials that used the same pain model, the same primary endpoint, the same 12-hour dosing schedule, and the same comparisons versus placebo.

This search yielded to similar randomized trials of Schedule II opioids, and it is noteworthy that this study had similar baseline demographics in terms of age, sex, race, and BMI, as well as similar baseline pain intensity scores to the phase 3 CTC study. Although historical analysis results need to be interpreted with caution, the fact that these studies had similar designs and patient populations suggest that it is reasonable to compare the results in order to gain insight into relative efficacy.

The two trials of Schedule II drugs evaluated either oxycodone or hydrocodone combinations with acetaminophen. Both drugs had immediate- and extended-release features and were administered every 12 hours, the same as CTC. The treatment effects on the primary endpoint for SPID through 48 hours are plotted here. Both

Schedule II drugs were efficacious, as you can see. The treatment effect for CTC in Study 301 was similar.

It is also worth noting that more than three-quarters of patients in each of the active treatment groups received rescue medication during the treatment period. The relatively high rates of rescue medications used in this study requires some discussion. These rates of rescue would be considered high if these were effectiveness trials, but it's important to recognize that these are efficacy trials, which are required for regulatory approval, as was pointed out by Dr. Gascon.

Efficacy trials do not fully reflect clinical practice because of the design requirements. For example, in the CTC phase 3 study, all background analgesia was removed from the patients the morning after surgery, and patients were only randomized once their pain scores increased to a moderate or severe level. This is not the way we practice in daily activities at the hospital.

The goal of efficacy studies is to isolate the analgesic effects of each of the study drugs. This is inconsistent with the principles of multimodal analgesia; that is treating patients with multiple analgesics to take advantage of multiple target receptors both at the peripheral and the central level, with the goal to, number one, provide improved analgesia and, number two, decreasing the incidence of side effects.

Therefore, it is expected that the rates of rescue breakthrough medications in efficacy trials be much higher than in clinical practice. Thus, cross-study comparisons suggest that the analgesic treatment effect of CTC was similar to the Schedule II combination products with regard to SPID and rescue medication use.

Regarding public health effects, CTC contains tramadol, a Schedule IV opioid with an inherently low potential for abuse and dependence. Therefore, it is reasonable to expect that CDC will provide a public health benefit if it was prescribed in place of higher scheduled opioids for

appropriate patients.

The final domain is risk management. If approved, CTC will be included in the class-wide opioid REMS. This REMS require that training is made available to all healthcare providers through unrestricted grants destined to fund continuing medical education and other elements to assure safe use. Pharmacovigilance is another essential risk management tool, which will be addressed by the sponsor should CTC be approved.

Finally, I would like to briefly discuss my views on how CTC should be used in clinical practice. As addressed by Dr. Viscusi, treating physicians are caught in a dilemma. We all want to reduce unnecessary opioid use. We are aware of the problem that we have been generating, but we also want to provide appropriate treatments for our patients. The sponsor's clinical studies have shown that CTC will be a viable treatment alternative to Schedule II opioids for many patients.

Today, tramadol is often overlooked in acute

pain management because of the perception that it cannot provide sufficient pain relief. That is why we see such high rates of prescribing oxycodone and hydrocodone as a reflexive action by discharging physicians after surgery.

CTC will be a new therapeutic alternative that provides more pain relief than tramadol with better tolerability and a comparable safety profile. Therefore, CTC will be a valuable treatment option for physicians to consider that would reduce the exposure of patients and the community to riskier Schedule II opioids. Thank you for allowing me to share my perspective, and I turn the lectern back to the sponsor. Thank you.

Clarifying Questions

DR. LITMAN: Thank you, Carlos.

Are there any clarifying questions for Esteve? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter, and I'll remind everyone if you have a question, put your name tag on its end, and we will try and get you guys in

order and call on you one by one.

Dr. Michna?

DR. MICHNA: Hello. I have to say I'm not a big fan of combination drugs being a former pharmacist. I think it complicates things, but I just had a few questions. What is going to be recommended to do for breakthrough? Are there going to be any recommendations?

DR. PLATA-SALAMAN: The treatment of any breakthrough pain will be based on the judgment of the individual physicians based on the characteristics of patient. In this regard, I will ask Dr. Leon to please explain how he would use CTC in the context of breakthrough pain and additional medication that the patients may need.

DR. DE LEON-CASASOLA: [Inaudible - off mic].

DR. LITMAN: Is the microphone on?

DR. DE LEON-CASASOLA: Now it is. His magic touch.

(Laughter.)

DR. DE LEON-CASASOLA: As it was alluded, it

is about individualized care. You are right, Dr. Michna. It's been hard to address how we manage medications that have two drugs included in the presentation, but this is what physicians are used to doing now with the availability of hydrocodone/acetaminophen and oxycodone/acetaminophen; so I think that will not be a big barrier.

Regarding the treatment for breakthrough pain in these individuals, I also believe that now the standard of care, based on multimodal approaches, will be that these patients receive acetaminophen on a scheduled treatment, around the clock, and if pain then appears, then an evaluation will take place to try to determine what is the source of the pain. So it will not be a set protocol to treat these patients. I think that this is critical.

DR. MICHNA: So what if the patient's at home? Now, do I give them an oxycodone script with this? How is that helping the situation?

DR. DE LEON-CASASOLA: No, I don't think

that that will be the appropriate --

DR. MICHNA: -- and what's going to prevent my patient from taking -- after an hour with your delayed onset, from re-dosing with the same drug?

DR. DE LEON-CASASOLA: This will be part of the education. Now, with the state regulations that mandate that patients go home -- with anywhere from 3, in the case of the state of Florida, to 7 days in the case of the states of New York and Massachusetts where you practice -- this will actually limit practices of increasing doses, what is called uncensored increases.

But I think that --

DR. MICHNA: You know, Oscar, come on, when patients go home, they're going to be doing everything. So what happens when you double or triple the dose? What kind of added risk here? We're having higher doses of celecoxib there on top of it, and you do have a little delayed onset with your first dose, right? The onset time to peak effect is a little delayed, and as a patient, if I'm exhibiting severe pain, and I'm waiting, and

it's an hour, the natural tendency is to take another.

DR. PLATA-SALAMAN: The --

DR. DE LEON-CASASOLA: I'm sorry, Dr. Plata. Go ahead.

DR. PLATA-SALAMAN: Related or what happens when you increase the dose, as presented, CTC contains a dosage that is less than half of the individual components. We have not tested more than 200 milligrams in the case of CTC twice a day. So in the case of CTC, it contains 176 milligrams of tramadol, which corresponds to 17.6 MME below the CTC threshold and 224 milligrams of celecoxib.

We have a model that if a patient goes against the label, in our proposed label, we specify that the dose and regimen of CTC should be 200 milligrams twice a day for the indication of acute pain for patients with pain severe enough to require an opioid. If a patient goes against the label, we have a model, the pharmacokinetics, based on all the information available, including what are the doses approved of tramadol.

What you can see in this figure is the tramadol 100 milligrams 4 times a day, which is the red line, corresponds to the approved maximum dose of tramadol per label. If a patient goes against the label and would take CTC 3 times a day or 4 times a day, the tramadol exposure is still within the range of the approved label of tramadol. In the case of celecoxib, it is the same thing. Here in pink, you can see the modeling of the exposure of celecoxib 200 milligrams twice a day. Again, if a patient would take twice or 3 times a day, it will still be within the range.

Similar results in the pharmacokinetic modeling were observed. If a patient will take 400 milligrams of CTC instead of the 200 milligrams per label, in all cases, the exposure of tramadol and celecoxib is expected to be within the range of the approval labels of the individual components.

DR. MICHNA: I don't think you've answered my question, but I'm going to go on. I'm still concerned about what we're going to do for breakthrough pain.

Can we go to slide CO-56? This might be a question for both you and the FDA, but what I'm concerned about is that you have the placebo dose in between, so we have the placebo effect of that dose. I'm not sure how this is going to mirror the real clinical situations when patients have to wait 12 hours to take something.

These patients were dosed every 6 hours, correct? So there's a placebo effect of taking that pill, whether they knew it was placebo or not, or suspected it. And you can see, you kind of get a downturn on the first thing, so there is some kind of response there. Do we think this scheduling, which I can't understand why it was done, could have a beneficial effect to your therapeutics?

DR. DE LEON-CASASOLA: You are completely correct. The design of the study was based on what was required for a liquid [indiscernible], weight-controlled study, with the doses and regimen. In this case, the regimen was based on the fact that tramadol alone needed to be

administered every 6 hours according to the label, 50 milligrams every 6 hours, which is an adequate dose for acute pain by label, and also it is used in the clinical practice.

Dr. de Leon did comment about the difference that exists of the approach used in the clinical trials compared to the real-world clinical practice. I would like Dr. de Leon to comment on this particular point regarding the question that you have on the regimen and opioid rescue.

DR. DE LEON-CASASOLA: I'm going to try to address your concern with breakthrough pain. In January of this year, we published a trial that demonstrated that contrary to what we have been thinking, and that is that opioids are needed in the postoperative period once patients are discharged, that this is not the case. After major cancer surgery, GYN, upper GI, and lower GI individuals, 90 percent of the cases received only acetaminophen and ibuprofen, and 85 percent of the cases were satisfied.

So it is about changing the setup that we

have that patients necessarily need opioids for breakthrough pain in the postoperative period. I believe, based on that trial, that this is not the case. I strongly believe that if a patient is treated within an effectiveness design, where they will receive this medication early enough, perhaps in the recovery room, then they go home with acetaminophen administered every 6 hours around the clock, this will be enough.

We give very little credit to acetaminophen, but there is very good data from the Cochrane studies that show that the current doses of 500 to 1000 milligrams could be as effective as Schedule II opioids in the postoperative period. We have decided to ignore that because it's very difficult to teach new tricks to old dogs, but that is the data there.

DR. MICHNA: Just one final question. Celecoxib is usually thought to be kind of a weak NSAID of all the NSAIDs. I was wondering why you picked that particular one since there was some -- the IV was dropped because I think it was

not as effective as they thought it was going to be because it was kind of a weak NSAID. Any response to that?

DR. PLATA-SALAMAN: We did thousands of studies with different molecules in different conditions. The only co-crystal that fit all the criteria, as was presented, was this co-crystal. It happens that it fulfills the full criteria of multimodal analgesia with celecoxib because this is the tramadol product that will have the anti-inflammatory component with different mechanism of actions.

The clinical results clearly show that both contribute to the efficacy, both tramadol and celecoxib, at the low dosages, which is a very key aspect in the multimodal analgesia for responsible pain management. Because it contains the lower amount of tramadol, which is another requirement of multimodal analgesia, to use a less amount of tramadol, in this case, less than the CTC threshold for relative low opioid dosage, we see that CTC is an alternative for the Schedule II opioids,

combining the analgesic with the anti-inflammatory effect that celecoxib provides. The co-crystal was defined by the chemistry of CTC.

DR. MICHNA: I'm sorry. One other thing. Are there going to be any warnings about concomitant use with antidepressants?

DR. PLATA-SALAMAN: We will use most conservative labeling, so the answer is yes because we will use most conservative labeling in CTC based on the labels of the individual components.

DR. MICHNA: Thank you.

DR. LITMAN: Just to remind you, in the interest of time, please stick to very specific clarifying questions.

Dr. McCann?

DR. McCANN: Hi. Mary Ellen McCann. This is for Dr. Viscusi. If you'll go to slide 20, I think in your presentation, you said the risks of abuse of tramadol are fairly low. They are, but they're still about one-third that of oxycodone. If you look at the percentage -- well, if you look at the absolute rate of injection abuse, for

tramadol, it's about the same as hydrocodone; and if you look at it as a percentage, actually a higher percentage of tramadol is IV abused than either hydrocodone or oxycodone.

So do you have any safety information about celecoxib in particular being injected?

DR. PLATA-SALAMAN: We don't have safety information. Celecoxib is known to not have abuse potential.

DR. McCANN: But in this case, it will be abused because they'll take CTC and presumably inject it.

DR. PLATA-SALAMAN: As you can see here, the hydrocodone lower rates are actually based on the fact that this is a hydrocodone combination. We don't have data in this regard, but I would like Dr. Richard Dart to actually explain his context about these results shown here.

DR. DART: Thank you. Rick Dart from the RADARS system, and please forgive me if I cough. I won't be shaking anybody's hands today. The hydrocodone is 27 in this case because hydrocodone

is not desirable for injection. Almost all the product that's actually sold commercially has acetaminophen in it, which makes it difficult to prepare for injection. So I would portray it as tramadol is as low as hydrocodone because hydrocodone is not a popular drug.

DR. McCANN: But it's still half of oxycodone. I mean, there's still a number there that's significant.

DR. DART: There is a number; I totally agree. If a patient were to take -- say double the dose of CTC and inject it, we don't have any information studying that. But knowing celecoxib, I wouldn't expect that to produce toxicity of that dose.

DR. McCANN: Yes. I think it would be helpful, at least for me, if there was even animal data demonstrating that injecting high doses of celecoxib is not causing renal damage or anything else. Thank you.

DR. LITMAN: Thank you. Just while we're on the subject, I wanted to interject there. I would

imagine the FDA knows it. There was a study from the British Medical Journal last May. The Mayo Clinic did a large database analysis of persistent opioid use after surgery, and tramadol was the same as oxycodone and hydrocodone.

Dr. McAuliffe, please?

DR. McAULIFFE: Hi. I want to go to your briefing document. You didn't talk about the subgroup analysis, the SPID data, but in looking at this -- well, looking at the sample, they were mostly white young women having bunionectomies, but looking at the data here, you have some males, some elderly, and some BMIs over 30.

They seem to fall outside of the SPID efficiencies. The older people seem to have -- and we know this. I think we have to scale down tramadol with elderly people, and this is less of a flexible drug to be able to do that with. But elderly people seem to have a much bigger effect, males have a much less effect, and the heavier patients more of an effect.

Are these going to be -- are you going to

advise that they are prescribed differently for these populations?

DR. PLATA-SALAMAN: No. As indicated in this data set, we can see that there is a significant overlap of the confidence intervals. As shown, we don't see any major difference related to a potential differential effect of CTC in these two groups, because, as you can see in BMI, both groups, there was efficacy. There was more efficacy in one of the groups. We cannot explain the reason for this, whether the BMI subjects were heavier. It could be just a finding by chance because we didn't analyze with the multiplicity of the data.

As it relates to the age, because of the type of pain model, as you can see, there is only a small number of elderly subjects more than 65 years of age. As it relates to this age, we identify that there is a significant overlap of the confidence interval. Adverse event profile is very similar compared to tramadol. Also, compared to later than 65 years of age, you have here the

results, CTC in blue, tramadol in red, later than 65 years of age, very similar safety.

On the right, also for objects more than 65 years of age, very similar. As it relates to the restrictions of dosing in the label for the elderly more than 75 years of age, the label specifies restrictions of 300 milligrams per day. CTC contains 176 milligrams. We are in full agreement with the analysis of the FDA, too, that in relation to the race difference and gender, the subgroup analysis did not show any specific trend.

So our conclusion is that we don't see a particular reason why CTC will have differential effects or different effects based on age, gender, baseline pain, and different ethnicities. We will follow the recommendations in the labeling, most conservative recommendations in the labeling, based on the individual components for the indication we propose for pain, for patients that have pain severe enough that require an opioid analgesic.

DR. McCANN: Thank you. But it does show a double-treatment effect for the elderly, minus 122,

minus 61. Thank you.

DR. PLATA-SALAMAN: Yes. With the number of patients that we have -- and again, the label will specify the dosing per the restrictions that exist currently in the tramadol labeling.

DR. LITMAN: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: A clarification for Dr. de Leon. Could you please expand on your comment regarding the efficacy versus effectiveness, and why do you expect the effectiveness to vary? It seems to me that if this is going to be a second option, alternative option if something else, acetaminophen or NSAIDs are not working, that you are also going to have in clinical practice the patients that are still at higher risk of course.

DR. DE LEON-CASASOLA: Sure, and thank you very much for asking. This is a critical issue because efficacy studies do not resemble the type of clinical activities that we implement in patients. For instance, in this particular study, the original anesthesia block was stopped, and the

patients were allowed to have an increase in their pain, which we know now creates a problem with peripheral sensitization, central sensitization, that may occur very shortly after that. We know that that translates in a higher consumption of analgesics in the postoperative period.

The concept now is to implement techniques that will prevent the conduction and transmission of pain prior to it occurring, and that is called preemptive analgesia with medications given prior to surgery, implementing technologies and treatments that will limit the bombardment of nociceptive impulses going to the central nervous system and then maintaining this level.

This is why an efficacy study will actually load up the potential for more breakthrough utilization and the potential for more pain than an effectiveness study, where you would prevent all these issues as such, then limit the amount of pain that they will have and the amount of breakthrough medication that will potentially be needed.

DR. LITMAN: Dr. Meisel?

DR. MEISEL: Steve Meisel. Three brief questions. First, slide 40, would you put that up, please? Could you explain to me why you don't have a column here for celecoxib? You have the CTC, you have the tramadol, you have placebo, but you don't have an adverse effect rate for the celecoxib alone.

DR. PLATA-SALAMAN: This study was done in Europe, and celecoxib is not approved for acute pain in Europe.

DR. MEISEL: No, but it just seems -- okay. Slide 43, we have a comparison here of CTC with tramadol alone, with celecoxib alone, and with placebo. Why don't we have an arm that has the combination of individual ingredients of tramadol and celecoxib? That's what you're really marketing this against, is the individual ingredients that would otherwise be given together versus a combination product, but you don't have that comparison.

DR. PLATA-SALAMAN: We could have had a combination there, but based on the conclusions of

all the crossover design studies that identify the effects of individual drugs, we concluded that the combination was not going to be safe or effective because the replicated profile of pharmacokinetics for celecoxib clearly chose impaired absorption of celecoxib with a combination. These were replicated in all these studies in the United States, outside of the United States, and also using different reference products, American and European reference products.

As well, the results where replicated clearly showed that the CTC tramadol profile clearly differentiated from the combination approach, which is indicated here, from tramadol of the combination approach, the black line, and that this profile of the reduction of Cmax and longer Tmax is fully consistent with the reduction of opioid-associated adverse events that we see with CTC compared to the combination.

This also is consistent with the tramadol label, which specifies that that there is a relationship between the increased plasma

concentrations of tramadol and the increased frequency of opioid-associated adverse events.

Therefore, taking into consideration all the information and data we have with the single and multiple dose and crossover design studies that did not have confounding factors, we decided not to include the combination in our phase 3 study.

DR. MEISEL: Well, that's your real marketing niche here is to say -- because people are using these two drugs in combination, and the unanswered question here is what's the real outcome versus real life, so let's move on.

Slide 51, briefly. You made the point here that CTC is better than tramadol and celecoxib, but I just want to clarify here, they're all better than placebo --

DR. PLATA-SALAMAN: Yes.

DR. MEISEL: -- but the confidence limits overlap here, and there is no statistical difference between CTC, tramadol, and celecoxib in this outcome. Is that correct?

DR. PLATA-SALAMAN: The primary endpoint was

met. What is here is shown the placebo-adjusted SPID, 0 to 48 hours. The primary endpoint was met because CTC by itself was significantly different to tramadol, to celecoxib, and to placebo.

Can I have slide CO-50, please? The primary endpoint, this is the primary without the placebo subtracted effect. At the bottom, the p-value difference, so CTC for tramadol, then for celecoxib and for placebo. So it differentiates from all three treatments.

DR. MEISEL: Okay. Slide 50 shows an overlap of confidence limits. Okay. Thank you.

DR. LITMAN: I apologize to those panelists that still had questions. We're running out of time, and we're going to hope to make up for it later.

Dr. Horrow, do you have a short question, a clarifying question?

DR. HORROW: I had a clarifying question on the posology of 200 milligrams twice a day. It has to do with slides number 36 and 38. The variable of SPID, 0 to 8 and 0 to 12, it could be that it is

statistically significant at 0 to 12 only because it includes the interval from 0 to 8, and there is no difference at 12 hours.

The clarifying question I have is do you have and can you show data from the 12-hour time period alone that indicates that, in fact, at 12 hours there is still a difference or are we just looking at a carryover effect from 0 to 8?

DR. PLATA-SALAMAN: This was a single-dose study that allowed us to choose the 200-milligram dose because it provided the maximum efficacy at closely 4 doses. In the phase 3 study, the 301 study, where it was administered every 12 hours for 48 hours, if we do the analysis of this SPID, 0 to 12, that also shows a statistically significant difference of CTC through all other three groups.

Based on the sufficiency or analgesia, with the fact that there was no need for additional oxycodone rescue medication toward the end of the 12-hour interval, the dose of 100 milligrams every 12 hours, it is adequate for the benefit of patients. Also, considering the dose of tramadol

that we use in this study, 50 milligrams 4 times a day, it is an adequate dose per label used for acute pain, and it is commonly used in clinical practice.

DR. LITMAN: Thank you. I apologize for the panelists that didn't get to ask questions. We will try and make up for it later on. I'm keeping your names here, so please keep your questions.

Now we're going to go to the FDA for their presentations, please.

FDA Presentation - Saranrat Wittayanukorn

DR. WITTAYANUKORN: Good morning. My name is Saranrat Wittayanukorn. I am the epidemiologist in the Division of Epidemiology. Today I will be presenting recent data on the use, misuse, abuse, and overdose of tramadol and comparator opioid analgesics.

The FDA draft guidance for the industry of opioid analgesic drug consideration for the benefit-risk assessment framework notes that FDA also considers the broader public health effects of opioid analgesic drugs. This involves

consideration of the risks related to misuse, abuse, opioid-use disorder, accidental exposure, and overdose for both patients and others.

The objective of this presentation is to inform the advisory committees regarding the public health risk-benefit of tramadol-containing product approval by first depicting patterns in the utilization of tramadol products and comparator opioid analgesics; and second, presenting epidemiologic data on the misuse, abuse, and overdose involving tramadol products and comparator opioid analgesics.

I will start with the use of tramadol and comparator opioid analgesics. For prescription utilization data, we used a database that measures the dispensing of prescription from outpatient retail pharmacies to patients based on transactions from a robust sample of retail pharmacies. Data are projected to provide national estimates of drug utilization. We ran these data for tramadol and commonly prescribed opioid analgesics, including hydrocodone, oxycodone, morphine, and codeine.

Since 2013, single-entity tramadol has been the second most dispensed opioid analgesic, and it's percentage among opioid prescription has increased. The figure shows the nationally estimated number of dispensed prescriptions for opioid analgesics from U.S. outpatient retail pharmacies, from 2009 to 2018.

Looking at the gray bars, we see that total opioid analgesics prescription peak at 2012, then decline. Overall, more than 95 percent of tramadol prescriptions was single-entity tramadol immediate-release or IR. The number of dispensed single-entity tramadol prescriptions gradually declined after the rescheduling in 2014, however, data showed that single-entity tramadol continued to be the second most dispensed opioid analgesic after the combination of hydrocodone and acetaminophen.

We also noticed an increasing trend in tramadol as a percentage of total opioid analgesic prescriptions, and you can see the percentages in the blue box above the blue line. In 2012, it is

around 14 percent, and in 2018, it is around 19 percent. Also, I would like to note that we will keep the colors consistent throughout the presentation, and the blue color refers to tramadol.

Before we go over data sources on misuse and abuse, here are the definitions of misuse and abuse used in this presentation, which are consistent with what the FDA has previously used in its guidance to industry.

Misuse is defined by the FDA as intentional use for therapeutic purposes of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Some examples are using more than prescribed, using more often than prescribed, and using someone else's medication for pain or for sleep.

Abuse is defined by the FDA as intentional, non-therapeutic use of a drug product or substance, even once, for desirable psychological or physiological effects. Abuse includes use to get

high. Also, non-medical use, this is not the regulatory definition used by the FDA, but it is used in some data sources and incorporates misuse and abuse as defined here.

Epidemiologic data sources on misuse and abuse focuses on a different characteristic of public health impact and also a different population. Therefore, we use a mosaic approach to consider these different characteristics and populations in a more informative assessment of the risk associated with misuse and abuse of tramadol and comparator opioid analgesics.

In the first column on the left are the characteristics that I will be presenting later in the following slides. For the scale of misuse and abuse, we rely on national representative surveillance system, and we also included vulnerable subpopulation in our assessment of frequency of misuse and abuse. We also looked at route of abuse because it can influence severity of medical outcomes.

Finally, we estimated morbidity and

mortality associated with misuse and abuse. We included 7 data sources from different populations, including the general population, individuals entering treatment for opioid-use and substance-use disorder, as well as people seeking care or advice. I will elaborate more about each data source and findings later in the presentation.

On to the scale and frequency of misuse and abuse; data from the general population showed that past-year misuse and abuse of opioid analgesics declined from 2015 through 2018. The speaker chose nationally representative estimates of the percentage of past-year misuse and abuse from the National Survey on Drug Use and Health.

The first cluster of bars showed there was a decline over time in misuse and abuse of any opioid analgesics, and I want to highlight that. It is consistent with tramadol and comparator opioid analgesics. As you can see, the percentages of any past-year misuse and abuse of tramadol among the U.S. population slightly decreased over time. For each comparator opioid analgesics, the percentages

also slightly decreased or remained stable. The most commonly misused and abused opioid analgesics were hydrocodone and oxycodone.

Similarly, a nationally representative study of U.S. high school seniors showed that across the study period, the percentages of high school seniors reporting past-year misuse and abuse of tramadol and comparator opioid analgesics appeared to decline or remained stable from 2014 to 2018. The data suggested that among high school seniors, the percentage of those who abused or misused tramadol products in the past year, as shown by the blue line, was generally lower than for comparator opioid analgesics.

The next data source, which is from people calling to our U.S. poison centers, showed that calls involving misuse or abuse of tramadol and comparator opioid analgesics declined from 2014 to 2018. Across years, there were relatively more calls involving oxycodone and hydrocodone misuse or abuse, while there were fewer calls involving morphine and codeine.

Data from individuals evaluated for opioid-use disorder or substance-use disorder showed mixed results, and I would like to give a brief overview of the differences between the two data sources. Both data collection networks are nationwide. Data from NAVIPPRO ASI-MV on the left came from a heterogeneous population of people being assessed or treated for various substance-use disorders. Data from RADARS TCP on the right are data from people presenting with opioid-use disorder and collected data on codeine for just a part of the study period. This is why we didn't show codeine in the RADARS TCP finding.

The results from NAVIPPRO ASI-MV on the left showed a decreasing trend in past-month abuse of tramadol and comparator opioid analgesics, however, results from RADARS TCP on the right showed that past-month abuse of tramadol increased, whereas past-month abuse of comparator opioid analgesics declined.

It is unclear why tramadol abuse appears to increase in RADARS TCP and more research and

confirmation are needed. One hypothesis is that RADARS TCP are from people with a more advanced opioid-use disorder compared with NAVIPPRO, which has a more heterogeneous population.

Another hypothesis is that tramadol may be relatively easier to get compared with Schedule II opioids, and it is also consistent with the finding from the drug utilization that I previously presented that showed an increase in tramadol as a percentage of total opioid analgesics prescriptions. However, the available data are insufficient to draw a conclusion about the mixed results.

On to the data on route of misuse and abuse, which is significant because it can influence the severity of medical outcomes, among calls to poison centers involving single-substance misuse or abuse, the oral route was the most commonly by far reported route of abuse of tramadol and comparator opioid analgesics.

Among individuals evaluated for opioid-use disorder or substance-use disorder, swallow whole

was the most commonly reported route of abuse of tramadol and most comparator opioid analgesics. The figure on the left shows data from NAVIPPRO ASM-MV and the figure on the right shows data from RADARS TCP.

In another analysis of this data, combination products tend to be injected less than single-entity products. Across two data sources and also consistent with data from poison center that I just previously presented, swallow whole was the most commonly reported route of abuse of tramadol and most comparator opioid analgesics, except for morphine.

In NAVIPPRO ASM-MV, injections, which are the green bars on the slide, was the most reported route of abuse of morphine. Note that the snorting and injecting routes were more common in this treatment center data than in poison center data in which the affected people did not necessarily have opioid- or substance-use disorder.

The final characteristics are estimates of morbidity and mortality associated with misuse and

abuse of tramadol and comparator opioid analgesics. Data from people calling to poison centers showed that, looking at the figure on the left, among calls involving misuse and abuse of tramadol as a single substance, related medical outcomes were categorized almost 50 percent of the time as having a moderate effect, which is defined in the textbox on the right as symptoms that were more prolonged or involved some treatment.

Other common categories were minor effects, which were less via severe medical outcomes and major effects. Similarly, on the right figure, finding from multiple substance exposure calls involving misuse and abuse of tramadol yields consistent results, except there were more deaths, which is the bar with 1.7 percent at top.

Here are nationally represented estimates of emergency department visits associated with nonmedical use of any prescription opioids. Looking at the pie chart on the left, the whole circle represents over 127,000 ED visits estimated annually, attributed to nonmedical use of any

prescription opioids from 2016 to 2017, and the dark portion represents tramadol and comparator opioids. These are further broken down into the stacked bar in the middle of the slide and is also further described by the figure on the right.

As you can see from the figure on the right, among ED visits involving nonmedical use of any prescription opioids, tramadol was relatively less common than hydrocodone, oxycodone, and morphine, but relatively more common than codeine. These are annual national estimates of opioid overdoses by opioid substance mentioned in the literal text of the death certificate.

Between 2011 to 2017, tramadol was less common than comparator opioid analgesics, and there was an increasing trend in tramadol-involved overdose deaths. We also see some increases in morphine and oxycodone over the study period with a decline in the most recent year of the data. But keep in mind that there are factors that may also have an impact on the number of deaths in this data, and I will briefly mention it in the few

slides.

To summarize, the recent trends in misuse, abuse, and overdose deaths across different data sources, most data sources suggest a down trend in tramadol misuse and abuse. Similarly for comparator opioid analgesics, misuse and abuse during the study period either remained stable or decreased. Of note, we saw some mixed results of tramadol abuse among people evaluated for opioid-use disorder or substance-use disorder. Also, data from death certificates suggest an increase in overdose death involving tramadol.

I want to briefly mention points to consider of data sources that showed an increase. For example, on the left, data from RADARS TCP are from people with more advanced opioid-use disorder and may not be generalizable to general population. On the right, data from drug involving mortality data, overdose deaths often involve multiple opioid substances such as fentanyl. Increased reporting over time from change in documentation may also have an impact on number of overdose deaths.

In summary, we can define the use, misuse, abuse, and overdose associated with tramadol and comparator opioid analgesics. The number of dispensed prescriptions of immediate-release tramadol single entity increased from 2009 to 2014, then gradually declined through 2018. However, the proportions of prescriptions dispensed for tramadol in relation to total opioid analgesic prescriptions increased during the study period, accounting for approximately 19 percent of total opioid analgesics in 2018.

In addition, across data sources, tramadol was less frequently implicated in prescription opioid misuse, abuse, and related morbidity and mortality than were hydrocodone and oxycodone. However, results were mixed for tramadol's position in relation to codeine and morphine.

Next, misuse and abuse of tramadol and comparator opioid analgesics have declined among general U.S. population in recent years, as observed in national surveys and in poison call center data, however, tramadol abuse may have

increased among people with advanced opioid-use disorder.

Finally, tramadol-involved overdose deaths increased from 2011 to 2017. The increases were also observed for oxycodone and morphine. However, other factors, including improved documentation as well as co-involvement of other substances, may be driving this observed trend. I will now conclude my presentation. Thank you.

Clarifying Questions

DR. LITMAN: Thank you. We will now take clarifying questions for the FDA. As before, if you could put your name tag on its side, and we will call on you.

Dr. Suarez?

DR. SUAREZ-ALMAZOR: Thank you. I realize that it's difficult to separate abuse and misuse from some of this data, but most of the FDA presentation I think reflects really abuse, which we know is less with tramadol. However, one of the concerns that I think may happen with this drug, especially in the postop setting, is misuse with

increased dosage than that recommended, and that would be an issue with celecoxib, and that has not been mentioned at all by the FDA.

We know what has happened with liver failure with a combination of opioids with acetaminophen, and I wonder if misuse of this drug could lead to increased complications with GI bleeding or cardiovascular events in patients using this combination in the postop setting. But it has not been mentioned as a concern at all by the FDA, so I was wondering what your thoughts were about that.

DR. STAFFA: Hi. Judy Staffa from the Office of Surveillance and Epidemiology. You're right. This presentation really focused more on the public health misuse-abuse issue. I don't know that we have specifically looked into the issues you've raised in the clinical trial program of this product because, obviously, you wouldn't see the increased dosage. But since tramadol and celecoxib are marketed products, I think those would likely be known safety issues.

DR. LITMAN: Dr. Green?

DR. GREEN: Thank you. Traci Green. I had a question with respect to slide 13 and the contrast and disparity between the NAVIPPRO and the RADARS system on the rates. I was wondering if an analysis that considered either one or two that might look at -- the ASI asks for the primary drug of abuse and for that to be indicated by the patient; whether a subset that looks at the primary drug of abuse where it's an opioid could help inform and look at contrast here, and look to see if there are similarities in those rates of tramadol abuse reporting, or to think about the NAVIPPRO system, since it's a heterogeneous one, to subset those that are OTPs, or opioid treatment programs, so that you have a little more comparability between the two, and look to see if these rates do increase or decrease in that -- I'm wondering if that analysis had been done.

DR. WITTAYANUKORN: Thank you for your question. We haven't looked at that, but later on after this presentation, we will take a look at it. Thank you.

DR. LITMAN: Dr. Setoguchi Iwata?

DR. SETOGUCHI: Related to the morbidity-mortality data, I was wondering if you have any data that could relate to the route of abuse and misuse for tramadol, because I still see IV and snorting in that data.

DR. STAFFA: I'm sorry. Could you speak into the microphone? We had trouble hearing your question.

DR. SETOGUCHI: Okay. So my question is about the morbidity-mortality data. I see that even though the majority of the abuse and misuse is occurring through oral use, I still see IV and snorting of tramadol. I was wondering if you can relate this morbidity-mortality data to the route of misuse and abuse of tramadol.

DR. WITTAYANUKORN: Thank you for your question. Right now, it's beyond the scope of our review; we haven't looked at it. But as you may recall the data from NPDS, it also has routes of abuse and also has severity of medical outcomes. Later on, we can try to look and certify the

medical outcomes by route of abuse.

DR. SETOGUCHI: Thank you.

DR. WITTAYANUKORN: Thank you.

DR. LITMAN: Dr. Mehta?

DR. MEHTA: Hi. I was wondering if you could give any additional detail regarding -- I think when we were talking on slide 15, you made a comment that said that data shows that single ingredient abuse-misuse is greater than combination products, if I heard you correctly.

So I was just wondering if you could maybe clarify further, recognizing that the amount of prescriptions for tramadol-acetaminophen is substantially lower than single- ingredient tramadol, but comparatively speaking, how do the rates of misuse and abuse look within that category of tramadol, comparatively when it's a combination product.

DR. RADIN: Hi. I'm Rose Radin with the Division of Epidemiology. Yes, we referenced actually an analysis that our colleague Matthew Daubresse did for the AC. That is this afternoon

on oxycodone, where he looked at different routes of abuse of hydrocodone- and oxycodone-containing products. The results of his analysis show that for hydrocodone and oxycodone abuse, there was relatively more abuse by the IV route of single-entity products.

So we were sort of extrapolating from those observations, and that was actually in reference to Dr. McCann's earlier question of the sponsor about IV abuse of a combination product. So I hope that clarifies your question.

DR. LITMAN: Dr. Zeltzer?

DR. ZELTZER: Thanks. The surveys that were looked at were surveys of opioid use and misuse, but in real life there are often combinations used, opioids with benzodiazepines, for example, which increase risk or with alcohol. I'm just wondering with the morbidity-mortality, if there are any combination surveys that are looked at, for example, tramadol used in somebody who abuses alcohol or who's on benzodiazepines.

DR. WITTAYANUKORN: Moon, could you please

bring the backup slides number 28?. Maybe now it's 29 or 27.

(Laughter.)

DR. WITTAYANUKORN: It's 28; sorry.

These figures, we looked at the multiple -- can you please advance to the next slide? Yes, okay, this is the slide that I'm going to talk about. On your question, yes, we did look at NPDS data and also looking at the concomitant of tramadol-involved other substances. As you can see on the slide, more than 25 percent of concomitant were prescription opioids, followed by benzodiazepines and alcohol.

DR. LITMAN: Dr. Horrow?

DR. HORROW: Thank you. I have a clarifying question, please, on the presentation of the summary in slide 23, please. That would be slide 23. Can we see slide 23? Thank you.

It says, "However, tramadol's percentage of total opioid analgesic prescriptions increased." I presume this is referencing slide 6. Could we see slide 6, please? Now, I noticed two things in

slide 6. The first is that the percentage of 18.7 indeed is greater than 13.6, but is this not also accompanying a rather interesting decrease in hydrocodone-acetaminophen prescriptions? So wouldn't this be good, that instead of prescribing a combination code 2 drug we're prescribing what became a code 4 drug?

Secondly, because the total number of prescriptions are decreasing, even though the percentage may have gone up, what has happened to the total number of prescriptions for tramadol? That might have stayed the same. We don't know that from this graph.

So my clarification question is what is the intent of using the word "however" in the summary slide? What is the point the agency is trying to convey?

DR. STAFFA: This is Judy Staffa. I can try to answer that question. I think you're right. What we're trying to do is to point out that the total volume of prescriptions, which you see is relatively stable, because tramadol may be more

available than other opioids, the drops we see in prescription volume are largely because of drops in Schedule II prescriptions, recognizing that the choice of what product I might choose to abuse may be a combination of what gives me the best effect, but also what's most available to me.

I think the point we were making by the "however" is that although we do not see dramatic increases in prescription volume of tramadol, it may be more available than others because it's now representing a larger percentage of opioid on the market than it did in the past, even though it's certainly not the majority.

Does that make sense?

DR. HORROW: Thank you.

DR. LITMAN: I just have one hopefully quick question.

Judy, the combination drug thing, like Ed was saying before, is a little worrisome. Does the FDA have any signals, not particularly with this kind of a drug, but going back years when people started to mix NSAIDs with opioids, that there are

any signals of increased toxicity from the NSAIDs due to abuse or misuse?

DR. STAFFA: This is Judy Staffa. We obviously keep an eye on that, but I think the fact that the combination products -- particularly if you think about probably the most frequently prescribed opioids like hydrocodone, the combination with acetaminophen was the most commonly prescribed.

We don't see as many issues relating to the injection of the hydrocodone combined with ibuprofen, but that may be because of the lesser availability; it's not prescribed as widely as the acetaminophen. So we don't really know whether it's because there's not a problem or because we're just not seeing it because of the lesser market share.

DR. LITMAN: Thank you. We do have a couple minutes before break, and I'd like to get back to some clarifying questions for the sponsor. Dr. Plata-Salaman, is that okay? I think Dr. Higgins has one question, and I know that other

people were waiting, and we'll try and get to you later on after the public session.

DR. HIGGINS: I think mine should be pretty quick. Jennifer Higgins. I was interested in learning more about the REMS preparation. There's mention of intending to have a REMS program, some healthcare provider education, and then like a consumer guide.

Can you provide any details about that and what your plans are?

DR. PLATA-SALAMAN: Yes, to monitor product use. In the case of CTC, we plan to enroll in the class-wide FDA analgesic REMS that includes making training available to healthcare professionals, including different opioid tools for facilitating identification of patients with certain characteristics; grants for continuing education; and other elements to assure safety use.

These will be complemented with the pharmacovigilance measures to also monitor product use, as well as other measures such as the tools of the RADARS and monitoring the database. This is a

tool, the REMS, from the FDA that we'll be involved with. Our approach will be that in using these tools, we will be able to monitor the product use for CTC.

As we explained, because CTC was designed originally to have significant improved efficacy to tramadol, because of the low dosages that it contains and the low MMEs, 17.6 MMEs, that could be an alternative option for Schedule II opioids within the indication that we are proposing, which is the same for tramadol, for the management of acute pain in others that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Therefore the REMS program will be very helpful to monitor its appropriate use for the right patients.

DR. HIGGINS: I wonder about the tools that you're talking about. It sounds like you're using something that is already provided by the FDA, or is it something that you're developing and have pilot tested?

DR. PLATA-SALAMAN: It is based on the FDA

REMS program that is applied to opioid analgesics.

DR. LITMAN: Thank you. We will now take a 15-minute. I apologize again to the other panelists who want to ask the sponsor questions, but we'll try our best to get you in a later. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume with the public session at 10:30 sharp.

(Whereupon, at 10:15 a.m., a recess was taken.)

DR. LITMAN: Welcome back. Before we start the public session, Dr. Staffa asked me to address -- the FDA has a point to address with the sponsor.

DR. STAFFA: Hi. Judy Staffa here. I just wanted to clarify something that came up in response to the last question from Ms. Higgins about the REMS. I just want it to be very clear that the committee understands, and I guess the sponsor as well, exactly what the REMS is. So I've

asked Somya Dunn from our Division of Risk Management, to just give a very concise summary, in a sentence or two, of what the opioid REMS is that this product would be joining.

DR. DUNN: Hi. I'm Somya Dunn from the Division of Risk Management. Just to clarify, the opioid analgesic REMS is a risk mitigation strategy that's designed to include all of the opioid products that are intended for the outpatient setting. This falls under that category, and that's why the requirement would be to join this REMS.

The main component of the REMS is an educational piece that's based on a blueprint that the FDA has worked on over the years and has also amended it over the years to try to keep up with the different components that we're trying to address in the opioid crisis.

Those educational pieces are aimed at all the healthcare providers that are involved in taking care of patients with pain and also is comprehensive of all different types of pain

management, from opioid analgesics to non-analgesic therapies, and those educational pieces are offered as CE that the companies are responsible for making available to providers. There's also a patient counseling guide that's also a part of the REMS.

DR. LITMAN: Did you have a clarifying question for the sponsor?

DR. STAFFA: No. This is Judy Staffa again. I just want it to be clear because I heard the word "monitoring" mentioned in the response to the question about the REMS, and I want it to be very clear that this particular REMS does not involve monitoring. If there is any kind of monitoring that would go on with this product, it would have to be through other mechanisms such as enhanced pharmacovigilance or postmarket required studies, et cetera.

DR. PLATA-SALAMAN: Thank you for your clarification. Yes, that's what I meant. When I commented on the pharmacovigilance tools and the databases for monitoring, monitoring product use.

DR. LITMAN: Jen, that's good?

DR. HIGGINS: I really appreciate that. That's very helpful. Thanks.

Open Public Hearing

DR. LITMAN: Okay. Let's start the public session.

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

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

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

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

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

Because we have a short meeting today and we need to get done by lunchtime, I'm going to ask that each public speaker is limited to 4 minutes.

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

MS. ZELDES: Good morning. Thank you for the opportunity to speak here today. My name is Nina Zeldes, and I'm here speaking on behalf of the National Center for Health Research, where I'm a senior fellow. Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

We have two major concerns about this drug and the study provided. In this factorial study, the combination drug is compared to a low dose of celecoxib, a non-addictive pain medication that doctors usually prescribe 400 milligram for the management of acute pain followed by an additional 200 milligrams needed. In other words, there's absolutely no evidence that this combination drug

with an opioid is as effective or more effective than a standard dose of just the NSAID.

Since this combination drug contains an opioid, it should only be considered for approval if it's more effective than a non-opioid painkiller. Combination drugs should only be approved when they have clear benefits that outweigh the risks of either the drugs alone. We know that some surgeons, for example, prescribe both opioids and NSAIDs after surgery.

Now that we know how quickly patients can become addicted to opioids, all opioids should be stopped within a few days, if prescribed at all, whereas if necessary, NSAIDs could be continued for a longer period of time since they are not addictive. However, if patients are prescribed this combo drug instead of two separate drugs, not only have they been introduced to an opioid, but they can't easily just stop the opioid while still getting the benefits of a non-opioid painkiller. They would have to obtain a non-opioid option instead of just having to stop taking one of the

prescribed drugs.

In addition to the above problems, the generic celecoxib and tramadol are likely to be much less expensive than a newly-approved combo drug and only the new drug is likely to be heavily promoted. The cost of medication is not FDA's concern, but FDA has expressed an interest in facilitating savings by approving generic drugs more quickly, and this type of unprovable combo drug with potential risks of addiction, which could replace the same generic drugs taken separately, is exactly why medical costs are so high. Thank you for your time.

DR. LITMAN: Thank you.

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

DR. GOTTLIEB: Good morning. My name is Dr. Ira Gottlieb, and I'm here on my own time representing Chesapeake Research Group. I am a principal investigator and owner of that center,

and I've had 25 years of clinical trial experience. I was the principal investigator on the pivotal phase 3-301 trial. Again, I'm here on my own time, and I have not received any financial remuneration for my visit today, nor do I have any financial interest in Esteve.

Our research site, Chesapeake Research Group, focuses almost exclusively on clinical trials that relate to the treatment of acute pain, most often postoperative pain, experienced in the outpatient setting. The bunionectomy model is a very common model used in our trials.

As we find ourselves in the present day worldwide opioid crisis, my staff and I have been focused on the treatment of pain and finding safer and less addictive alternatives used in the treatment of pain, again, for the past 25 years. Certainly over this time, the landscape of drug development has certainly changed. My early work was primarily in the development of the COX-2 selective nonsteroidal medications. They included Celebrex, Vioxx, and Bextra.

When the cardiovascular adverse events were identified in this class, the COX-2 development program came to an abrupt end; then the focus turned to narcotic reformulation and a change in the way the drug was delivered to provide a more steady-state continual dosing, eliminating the peak and trough related to the use of frequently dosed opioids. When the opioid crisis itself was identified, this pipeline, too, came to a screeching halt.

Next was the trend towards multimodal therapy using nonsteroidal medication: Tylenol, antiseizure medications, antidepressant medications, along with narcotics to hopefully reduce total narcotic use. Currently, the trend seems to be in the development and reformulation of local anesthetics to greatly prolong their effect.

As the principal investigator of the Esteve pivotal phase 3-301 study, I come to you today, again, on my own time and expense from nearby Pasadena, Maryland, where Chesapeake Research Group is located. I have been the principal investigator

on nearly 100 clinical trials, the vast majority of which focus on compounds being tested to treat acute and postoperative pain experienced in the outpatient setting. I greatly appreciate the opportunity to share my clinical experience and thoughts regarding this unique co-crystal compound developed by Esteve.

Each of the ingredients in CTC have been prescribed for many years, tramadol since 1977 throughout Europe and later approved for use in the United States in 1995, and celecoxib was approved in 1998. Though there are two primary ingredients, tramadol has in and of itself three mechanisms of action: a mu-receptor agonist, a serotonin, and norepinephrine reuptake inhibitor cell; celecoxib, a specific COX-2 inhibitor, nonsteroidal anti-inflammatory medication.

Tramadol by itself is strongly hydrophilic, which when taken by itself is associated with a higher incidence of opioid-related adverse events. The CTC crystal slows this rate of absorption and should reduce the incidence of opioid-related

adverse events. Further, tramadol, it should be emphasized, is a Schedule IV narcotic and has a much lower abuse potential and is one of the least desirable narcotics by abusers seeking a euphoric effect.

Celecoxib by itself is extremely hydrophobic, a contributing factor to its reputation as not one of the stronger nonsteroidals. CTC actually increases this rate of absorption and should increase its effectiveness more quickly than the celecoxib alone. Further, its COX-2 specificity makes it a desirable choice of the numerous nonsteroidals on the market based on its relative favorable GI AE profile.

In closing, the union of these two unique and multifunction medications is, in my opinion, a desirable choice as a single, easily understood dosing regimen that would likely improve patient compliance as compared with being told to follow a regimen of three or four different medications. Finally, I greatly appreciate this opportunity you've given me to speak at today's meeting.

DR. LITMAN: Thank you.

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

DR. GREEN: Hi. My name is Dr. Jody Green. I'm the chief scientific officer at Inflexxion, an IBH company, and while my travel is being reimbursed by Esteve, I am here on my own time to share some insightful real-world data regarding nonmedical use of tramadol from our proprietary database, ASI-MV. These data from ASI-MV have already been presented in FDA's comments earlier, and I think they did a nice job of illustrating the importance of looking at these data relative to alternative therapies, relative to the other opioid products that are most often prescribed.

In addition and to bring that point home, we did our own analysis, which was data from 2015 through 2019, and compared prevalence of the past 30-day tramadol nonmedical use to oxycodone IR products and hydrocodone IR products. What we saw

was that tramadol nonmedical use is endorsed in about 2 out of every 100 assessments that are completed, while hydrocodone IR and oxycodone IR are endorsed in about 8 out of every 100 assessments; so that's four-fold difference.

When we look at adjusting that for drug availability in terms of how much is dispensed at outpatient pharmacies, we see that difference increase to about a 17 to 19-fold difference in that oxycodone and hydrocodone IR nonmedical use, 17 to 19 times higher than that of tramadol in that program.

Unlike most of the medications, the route of administration reported for tramadol nonmedical use was primarily as swallowing a tablet whole, so no physical manipulation of the product in that instance. Tramadol nonmedical use is reportedly used in nonoral routes as well, as we also saw presented earlier.

Second, [indiscernible] were all remarkably less common for tramadol than for oxycodone IR nonmedical use, and oxycodone IR had the highest

rate of snorting; so 6 times higher than tramadol. In relation to the hydrocodone IR products, it was most likely reported to be used via chewing twice as likely than tramadol and snorting was over 3 and a half times higher for hydrocodone IR than tramadol.

We did have some conversation about the hydrocodone IR combination products, and what we see are low rates of injecting and smoking along with the low rates for tramadol. We know that the combination products, in general, are less likely to be injected or smoked due to the undesirability of the second active pharmaceutical ingredient and the effort it takes to separate the opioid.

So whatever you take away today, the evidence from these large real-world data sets illustrate that tramadol is most likely to be use nonmedically, and when it is used nonmedically, the user is typically not physically manipulating the product to use via nonoral routes. The abuse risk for tramadol as an active ingredient is significantly less than hydrocodone IR and

oxycodone IR.

Lastly, we know that the combination products offer an additional deterrent, if you will, for most users that are looking to get high or to abuse these products. So in my opinion, the product under review today does have a more favorable abuse profile, based upon both the active ingredient and the fixed combination, than hydrocodone IR and oxycodone IR, which are the most common opioids prescribed today. Last but not least, keep in mind that all of these medications do serve a therapeutic purpose and are important medications for all patients. Thank you.

DR. LITMAN: Thank you.

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

DR. COLEMAN: Good morning. I am Dr. John J. Coleman, a retired assistant administrator of the Drug Enforcement Administration, DEA. I appear here today at my own volition and expense. I have

no conflicts of interest and no financial relationships with the sponsor or any pharmaceutical company. I represent only myself and my views, which I will offer here. They are mine and mine alone.

I spent 33 years at DEA and its predecessor agencies. My responsibilities as assistant administrator included supervising the Office of Diversion Control, the DEA division that regulates and registers persons and business entities authorized to manufacture, distribute, prescribe, and dispense medicinal controlled substances. This also was the division that schedules drugs, including medicinal control substances.

The combination drug under review here today contains tramadol, a Schedule IV controlled substance. As you've heard, tramadol was FDA approved in 1995. Although classified as an opioid, its abuse potential at the time was considered minimal and below the levels requiring scheduling by the DEA.

Almost two decades later in 2014, after a

re-evaluation showed modest levels of abuse, FDA and DEA agreed to place tramadol in Schedule IV of the Controlled Substances Act. Schedule IV is defined in the statute as having, quote, "low abuse potential for abuse relative to drugs or other substances in Schedule III," unquote.

For at least the last or past quarter century, tramadol has been used in the United States as an effective analgesic. During this time, millions of prescriptions have been issued and dispensed for it. It's lengthy record as a beneficial medicine and a control substance is well known.

National systems that attract drug-related morbidity and mortality show relatively low levels of misuse of tramadol compared to levels observed with most other opioids. In short, tramadol remains well within the boundaries established by Congress to identify Schedule IV controlled substances. Schedule IV, by the way, is the next to last, lowest level for assessing and designating abuse potential of controlled substances.

Before I finish, I would like to say a few words about drug schedules. Having worked in this field for many years, I have encountered patients, caregivers, and even some practitioners who confuse and opioid's class or schedule level with its effectiveness as an analgesic. In this discussion, it's important to understand that the statutory requirement and sole purpose for scheduling medicinal drugs is to identify their potential for abuse.

Most medicinal opioids are on Schedule II, a designation indicating a high potential for abuse. The difference in abuse potential between drugs in Schedule II and drugs in Schedule IV is significant and worth considering in the review of this tramadol combination drug.

As has been noted, we are in the midst of an opioid crisis, and opioid abuse crisis. According to the CDC, drugs that are most frequently involved in opioid-related overdose deaths are Schedule I illicitly manufactured fentanyl, fentanyl analogs, and heroin, and Schedule II medicinal opioids such

as oxycodone, methadone, and hydrocodone. According to the Controlled Substances Act, drugs in Schedule I and Schedule II have the same abuse potential. However, in the case of Schedule II drugs, the FDA has determined that the benefit-risk ratio favors their approval.

These drugs, however, are in a category Schedule II that requires, quote, "severe restrictions." Some of the severe restrictions required by law may at times inadvertently and adversely affect a patient's access to these drugs. As mentioned, tramadol is a Schedule IV drug, meaning its potential for abuse is relatively low compared with the aforementioned Schedule II opioids. In addition, the severe restrictions imposed on Schedule II opioids do not apply to controlled substances listed in Schedules III, IV, and V.

Given my five decades of professional experience in the field of drug abuse control, I do not hesitate to recommend to you the approval of this innovative tramadol formulation that offers an

effective and low-abuse alternative to the highly abusable Schedule II that are driving the current public health crisis. Thank you.

DR. LITMAN: Thank you.

Will speaker number 5 please step up to the podium and introduce yourself, and please state your name and any organization you are representing for the record.

DR. LYON: Good morning. I'm Dr. Edd Lyon. I have no financial interests with or remuneration from the company producing this medication. The company did cover my transportation and lodging in order for me to be here. My testimony is purely voluntarily on my part.

In brief, my background is that of a small town family medicine physician in a rural town in Vermont. I practiced for 38 years, retired from there, and have been working in outpatient VA clinics for the past three years.

During my time in medical practice, I've borne witness and treated many patients who've been ravaged by our current opioid addiction epidemic.

This problem has obviously caused an unimaginable number of deaths and destroyed many lives. It's only been within recent time that the medical system has taken real initiatives to try to deal with this plague upon our country.

There are many interventions that can and are now being applied across this cycle of addiction. In my opinion, one of the more effective efforts we could make in this cycle is at the start, trying to prevent the acute pain developing into chronic pain and addiction. Many of my patients I feel have been treated either improperly or with excessive medication for their acute pain, which then leads to chronic pain and opioid addiction.

Examples include numerous instances of young athletes with an acute athletic injury treated with excessive amounts of opiates, which then lead to years and years of life-destroying addiction. Likewise, I commonly see this regarding low back pain and osteoarthritis being treated inappropriately.

I feel that this novel combination medication can become a welcomed addition to our toolbox for dealing with acute pain; certainly not the only one and maybe not the best one in each patient, yet I feel it becomes a new tool that is available. Also in my experience in prescribing tramadol and celecoxib, I find they've been both effective for relief of pain and have less addiction potential.

In treating the VA population, I've been particularly troubled by the effects of the opiates upon them. This is a population who has lived in harm's way and have widespread physical and mental pain. I have noted that in an attempt to deal with their acute pain, based upon the methodologies available at the time, these men and women were treated, yet had unresolved pain and soon joined the ranks of the chronically addicted opiates.

To its credit, the VA is working hard to introduce new protocols to deal with this tragic outcome. Despite this, the intersection of PTSD, depression, chronic pain, and opiates have been a

continuing nexus of epidemic suicides and troubled lives within the VA population. Incidentally, I would say most of the opiates that are being abused in this population are either hydrocodone or oxycodone. I seldom see tramadol being misused.

Again, I feel a new way of dealing with acute pain would be a welcomed addition to our armamentarium. Thank you for your attention.

DR. LITMAN: Thank you.

Will speaker number 6 -- and this is our final speaker -- please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. FUGH-BERMAN: Good morning. I'm Adriane Fugh-Berman, physician and professor of pharmacology and physiology and family medicine at Georgetown University Medical Center. I'm representing Pharmed Out, a rational prescribing project at Georgetown and also Physicians for Responsible Opioid Prescribing. My conflict of interest is that I'm a paid expert witness at the request of plaintiffs in litigation regarding

pharmaceutical medical device marketing practices, including opioids. This testimony is independent of that.

We oppose the approval of this new drug application for a fixed-dose product. Tramadol is interesting but a very unpredictable drug because of the individual differences. In CYP2D6, the opioid effect of tramadol varies widely. It will have no analgesic effect at all in 7 percent of the population with a deficiency of CYP2D6, and it will have a superpotent effect on about 10 percent of the population that are ultra rapid metabolizers. Every prescription written for tramadol, then, will have unpredictable effects.

Like other opioids, tramadol can cause respiratory depression and death, and because of differences in CYP2D6, it can cause respiratory depression at much lower doses than expected, especially in children, a population in which the FDA has specifically warned against using tramadol.

Not only does tramadol have the same adverse effect profile as other opioids, but it has

additional adverse effects. Because of its effect on serotonin and norepinephrine receptors, it can cause serotonin syndrome and hypoglycemia, especially in type 1 diabetics, and then it seems to have some unique adverse effects not associated with either opioids or SNRIs usually, including seizures, hyponatremia, QT prolongation, mania, and there are case reports of pica and Parkinsonism. Factors are also more common in tramadol users.

Although this drug is to be approved for acute use, it's very predictable that it would also be used chronically. By the way, it's also associated with bleeding ulcers, and it can cause drug interactions, especially when taken with any CYP2D6 inhibitors, which include of course many common antidepressants.

There are withdrawal syndromes, of course, that are associated with opioids and also serotonin reuptake inhibitors, but tramadol has an atypical withdrawal syndrome that can include panic attacks, hallucinations, and paranoia, and these are common. They occur in about 1 in 8 patients withdrawing

from tramadol. It's extremely worrisome that tramadol prescriptions have increased as a percentage of prescribed opioids, and the reason for that may be because physicians believe that tramadol is not an opioid or a weak opioid. This is a misperception, but many doctors do not believe this is an opioid.

There are two studies that have associated tramadol with increased mortality, including an observational study in osteoarthritis patients, and it found an increased risk of mortality compared to four common NSAIDs.

There's no question that tramadol is addictive. Among short-acting opioids, tramadol appears to be associated with long-term opioid use more often than other short-acting opioids. Dr. Litman referenced one study in the BMJ. There's also a 2017 CDC study showing that about 14 percent of those prescribed tramadol were still taking an opioid a year later.

Tramadol abuse is common. This has been much better demonstrated, though, in other

countries than in the U.S. Tramadol addiction is a major issue in India, Africa, and the Middle East. For example, 12 percent of Egyptian college students use tramadol. This is a huge problem elsewhere; let's not have it become a huge problem here.

It's very curious that the results of the two efficacy trials conducted by Mundipharma of this drug, including a trial in 726 patients after third molar extraction and another 1,138 patients after abdominal hysterectomy -- these were mentioned in the FDA briefing document -- are not included in this assessment. I wonder if that's something the committee could ask about; surely it's relevant to know about these acute pain trials.

It's unclear whether tramadol is actually effective for relieving pain maybe because of its wildly varying effects in different people. It's failed to show effectiveness for pain against NSAIDs, and in some cases placebo, in numerous clinical trials, including trials in

osteoarthritis, acute muscular pain, and third-molar surgery, which is commonly used for acute pain.

DR. LITMAN: I'm sorry. I'm going to have to cut you off. The time is running out, and we're trying --

DR. FUGH-BERMAN: Can I just --

DR. LITMAN: One last statement.

DR. FUGH-BERMAN: -- do my closing statement?

DR. LITMAN: Please.

DR. FUGH-BERMAN: We ask the committee not to approve this fixed-dose combination of tramadol and celecoxib because there's no evidence that the mixture is more effective than unilateral [indiscernible] doses of celecoxib or the product's components taken together.

The inclusion of tramadol increases risks without adding benefits, and given the widespread belief that tramadol is not an opioid or very weak, combining tramadol with an NSAID will only enhance misperceptions of benignity and will lead to more

opioid prescriptions and more opioid related harms. Thank you.

DR. LITMAN: Thank you.

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

Now, Dr. Lowy will provide us with a charge to the committee.

Charge to the Committee – Naomi Lowy

DR. LOWY: I will now shift the focus back to our asks of the committee. I will detail the two discussion points and one voting question for the committee to address. We asked the committee to consider the information provided to you in the background documents, the presentations, the clarifying questions, and the open public hearing, so I will go through the discussion point number 1.

Considering the abuse potential of tramadol 44 milligrams and celecoxib 56-milligram tablets

and its proposed use for the management of acute pain in adults that is severe enough to require an opioid analgesic, and for which alternative treatments are inadequate, please discuss any concerns you have regarding the impact of this product if approved on public health.

Discussion point number 2, discuss whether the benefits outweigh the risks for the proposed indication. Discuss if any additional data are needed for this application to be approved.

Finally, your voting question is do you recommend approval of tramadol 44 milligrams and celecoxib 56-milligram tablets for the proposed indication of the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Thank you.

DR. LITMAN: Thank you, Dr. Lowy.

We will now 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.

The other comment I wanted to make is I know that we have a couple of industry reps with specific expertise in both clinical trials and safety, and although you are nonvoting, the committee would be interested in your comments or responses to the questions.

Moon, can I have that first question again? Can we post that for everybody to see, please?

Again, I'm just going to repeat. Considering the abuse potential of tramadol and celecoxib and its proposed use for the management of acute pain in adults that is severe enough to require an opioid analgesic for which alternative treatments are inadequate, please discuss any concerns you have regarding the impact of this product, if approved, on public health.

This first question is just concerns about public health, and we'll get to the other part with question 1.

(Brief pause.)

Clarifying Questions (continued)

DR. LITMAN: Thank you, Moon, for reminding me. We have about 10 minutes to go back to the sponsor, if that's okay. There were a couple of panelists who did not get their questions in, and thank you for reminding me because I did want to get to that.

Professor Phillips?

MS. SHAW PHILLIPS: Thank you. My question actually related to our last open hearing speaker, and that was any data that you had looking at safety, efficacy, as well as the PK on rapid metabolizers or slow metabolizers, and subanalysis of the data or any comments related to that.

DR. PLATA-SALAMAN: We will use more conservative labeling regarding the drug-drug interactions --

MS. SHAW PHILLIPS: The question is not about labeling; the question is about data that you have or analysis of the data that you collected that would tell you about differential risk versus benefit in those subpopulations.

DR. PLATA-SALAMAN: The data that we have from all the crossover design studies that are included in the briefing document, the pharmacokinetics did not reveal any concern regarding any differences in the pharmacokinetics comparing tramadol alone or the tramadol plus celecoxib combination, and the differences with CTC were consistent in all the studies. We didn't do genotyping for 2D6 or 2C9 metabolites, so we do not have genotyping on the subjects that were used. Those studies in aggregate, all the studies concerning the crossover and clinical pharmacology studies have more than 200 subjects.

DR. LITMAN: Thank you. Dr. Zeltzer?

DR. ZELTZER: Thanks. One question that you didn't address is what percent of patients in your study, when you ended this study since it was a short monitoring period, continued to have pain and continued to use some sort of analgesic? Because there's a subgroup that will go on beyond the expected acute pain postop period and continue to have pain.

DR. PLATA-SALAMAN: As was shown with the oxycodone rescue medication in the 48-hour period, it can be seen that the percentage of patients using rescue medication over that period is low, and toward the end it's actually lower in the 12-hour intervals. Here, the 48 hour, which is the period where patients were monitoring with 33 pain score measurements, the oxycodone rescue by that time was already very low as indicated in this slide.

I would say that also, to answer that clarifying question, this slide referring to the treatments, whether they need additional treatments -- but to answer the clarifying questions regarding the every 12-hour dosing interval, the question that was in the morning regarding the 201 study of whether the effect was seen, the data was carried over the 12 hours, and this is actually the data that shows that it's not only that the effect maintains at 8 hours, but it extends to the 12 hours.

As it relates to any other medication that

patients may have in the subsequent days, 9 days after study, that was to the discretion of physician. But maintaining clarity on the oxycodone use, the overall profile of safety, which is important, considers all the adverse events of patients that received rescue medication, concomitant medication. But we do agree with the conclusion from the FDA that the safety of CTC is expected to be comparable through the safety of the individualized components within the context that CTC contains less than half of each of the individual components. And as it relates to tramadol, these correspond to less -- is below the CTC threshold for relatively low opioid doses.

DR. ZELTZER: But you didn't monitor the group that at the end of the 48 hours continued to have pain, and even though this study drug wasn't available, may have continued on separately since they couldn't access the combination, the celecoxib and the tramadol. Then looking at risk-benefit, if the combo drug, if your drug, were available, would they continue that beyond, and what would be the

risks of continuing that?

That's one question, then the other is pre-meds that patients may have been on, like duloxetine and SSNRIs that could impact toxicity potentially of tramadol or the tramadol component.

DR. PLATA-SALAMAN: The clinical trial design did include, as it relates to inclusions and exclusions, the warnings and contraindications per the individual labels. Patients were contraindicated based on certain characteristics because of medications that they were taking or based on the tramadol label or celecoxib label.

The clinical trial design followed the individual label's recommendations as it relates to contraindications, warnings, and precautions in relation to inclusion and exclusion. At the same time, this will be the same that we expect in the clinical practice because the same warnings, precautions, and contraindications will be included in the label.

DR. ZELTZER: So you don't know, just lastly, if this were approved, the number of

patients or percentage, following an acute surgical procedure, that would continue to use your medication continuously for a much longer period of time, and then what would be the risk-benefit ratio of that continued use for that subgroup?

DR. PLATA-SALAMAN: We will use monitoring for product use, and it would be based on the indication we proposed, for patients that require an opioid analgesic. As it relates to your pertinent questions regarding patients with other medications or adverse events, concomitantly or -- we have clinical experience on the safety of tramadol with other medications. I would like Dr. Viscusi to please explain his own experience of using tramadol in the clinic and also to clarify that question in the morning --

DR. LITMAN: Dr. Plata, I'm really sorry. I'm just going to take clarifying questions and not just opinions and conjecture. We may have time for one more.

Dr. Goudra, do you have a clarifying question?

DR. GOUDRA: Yes. Thank you. Basavana Goudra. If I can draw your attention to slide 28, if I look at the plasma concentrations, I almost get an idea -- at the end of 2 hours, for example, it looks like mean tramadol on its own, 100 milligrams, was around 280 nanograms, whereas in combination it was about 180 nanograms.

I wonder whether this new mixture is actually hindering the absorption of tramadol; that's one thing. And as it is, I wonder whether the therapeutic concentrations -- I don't know what other therapeutic concentrations, if you can tell me that. Finally, because the concentrations achieved are not even sufficient, whether the clinical efficacy that's been achieved is purely because of your hindsight.

DR. PLATA-SALAMAN: To answer your question, first, this is a co-crystal effect. Tramadol is a very highly soluble molecule, and the co-crystal structure because of the changes of the physicochemical properties, you reduce its intrinsic dissolution rate, that translates to

slower absorption.

What we see here is the co-crystal effect, but still tramadol reaches the level that are required for analgesic efficacy.

DR. GOUDRA: Can you tell me what's the therapeutic concentration?

DR. PLATA-SALAMAN: The threshold for therapeutic efficacy for tramadol will range from 125 nanograms per milliliter and above, and perhaps even lower, so it's very clear within that. The CTC effect also accelerates the absorption of celecoxib because celecoxib is an insoluble molecule. The synchronization both in the CTC and in the pharmacokinetics of celecoxib, you will see that it is an accelerated absorption from 3 hours of celecoxib alone to 1.5 in the pharmacokinetics. The blue line is indicated here.

So this more rapid absorption of celecoxib is synchronizing with the activity of tramadol for the efficacy. This is the model that we think is happening because we do see that in the phase 3 trial compared to 50 milligrams of tramadol 4 times

a day, which is a typical use of tramadol used in acute pain in clinical practice. We accelerated the meaningful pain relief by 53 minutes compared to tramadol alone.

DR. GOUDRA: Well, considering the pharmacodynamic variability, don't you think there could be some patients who are not even achieving therapeutic efficacy?

DR. LITMAN: I'm sorry. I'm going to cut you off. I just want clarifying questions. I apologize for. We're out of time.

DR. PLATA-SALAMAN: Dr. Litman, one clarifying question regarding the British Medical Journal article, can I ask Dr. Viscusi to present his analysis?

Questions to the Committee and Discussion

DR. LITMAN: No, I'm sorry. I've just been told that we don't have enough time for -- just clarifying questions.

Let's start the discussion. Again, just going back to question 1, there's no need to read it again, but I just wanted to remind everybody

this is on the public health concerns of this medication. Dr. Horrow?

DR. HORROW: Jay Horrow. There was some discussion about the potential toxicity of injecting this drug in terms of the celecoxib component of it, and I thought that I might provide some information regarding that.

First, you should know that my company, Bristol-Myers Squibb, has not produced an NSAID, as far as I know, since 1992, and that was just to market on the UK market, so I believe there's no conflict. The idea of diverting this medication for IV raises the issue of cardiovascular toxicity by one of the members of the panel. To my knowledge, the cardiovascular toxicities of NSAIDs are related to chronic use, not episodic injection or episodic use of these medications.

The chronic use, the cardiovascular toxicity is related to small increases in blood pressure perhaps that are maintained for long periods of time that then result in adverse cardiac effects. I would also point out that Steve Nissen's article

in the New England Journal of Medicine indicates that those toxicities are noninferior when compared with other NSAIDs, in particular with naproxen and ibuprofen.

Regarding the GI toxicity aspect of it, celecoxib has risks that are approximately half those of naproxen and ibuprofen. Again from the same New England Journal of Medicine article, the toxicity is GI toxicity, that is gastritis, which can lead to bleeding, but that is not the catastrophic liver failure that occurs with large doses of acetaminophen that could be administered, say, if someone were taking large doses of one of the combination products with hydrocodone or oxycodone.

Regarding the tramadol component of abuse in this medication, I would think that someone attempting such would just go for the tramadol tabs instead. It would be a far better choice than the fixed-dose combination. I see the potential for abuse much less than that with tramadol, and I think that this fixed-dose combination in regard to

the long-term public health aspects would be an incremental improvement over what's available now. Thank you.

DR. LITMAN: Thank you. I'll just remind everybody, we have an unusually large number of panelists today, so try and make your point shorter than usual. Dr. Hoffer?

DR. HOFFER: Thank you. Lee Hoffer. Just to give you some context, I exclusively work with people who abuse drugs, inject both illegal drugs and pharmaceuticals. Tramadol has been around forever, Ultram, and we hear about it a fair amount. But for people that I work with, they escalate their doses fairly rapidly, far beyond the MMEs associated with Ultram. They're much more interested in getting oxy, or fentanyl, or heroin, and you almost never hear -- you hear about Ultram about as much as you hear about codeine. That's point number one.

The second is that the charge to the committee is, I think, an important one to think about. If we're talking about opiate analgesics as

alternative treatment or the last line of other kinds of therapies, I'm not sure if it's fair to compare CTC to even tramadol, primarily because of the low dose here. When we look at the epidemiology of the challenges associated with tramadol, this drug isn't even tramadol; it's sort of tramadol light, if you will.

So I think, going back to a comment that was made earlier when we were talking about people giving opiate medications to control pain to patients, we want to start with the lowest dose possible to get an effect. So I guess for me, interested in public health and not wanting to see all the people that I -- well, not all of the people. A lot of the people that I work with started out as pain patients.

So I think here, there might be a nice balance. This is about as low a dose as you can probably still make a drug. I think that needs to be considered in the approval of this medication.

DR. LITMAN: Thank you. Dr. Zacharoff?

DR. ZACHAROFF: I actually didn't have a

comment, but I just want to agree with what Dr. Hoffer just said. I consider this to be a drug that is really a tramadol light, and I would look at it as something that carries less risk than tramadol.

DR. LITMAN: Thank you for your non-comment.

(Laughter.)

DR. LITMAN: Professor Phillips?

MS. SHAW PHILLIPS: I just want to comment on the difference between real-world use and ideal use. In 2014, we rescheduled a recommended rescheduling of hydrocodone, and it was very common among prescribers and the public to think that that was a much safer option. That was the same year that tramadol became a Schedule IV, and I know there are petitions to make it a Schedule II.

So I think we need to be careful not to say it's a better option. I think if the patients were all genotyped and it was limited to a couple of days use, and there were some parameters for safe use, it could potentially be a safer alternative for the right patients.

I think we just need to be careful in the context that we look at it as a niche. The public health concern I would have is for broad thoughts that it's a safer alternative.

DR. LITMAN: Thank you. Dr. Staffa?

DR. STAFFA: Judy Staffa. I just want to clarify what we know about the cardiovascular risk associated with NSAIDs. It actually is not limited to chronic use. There is no dose without risk, and that's in our labeling that was updated several years ago. Also, we are unable at this point to cleanly differentiate the risk associated with different agents, which is why it's a class-wide warning right now until we get further data on that issue. So I just wanted to make sure that was in the record.

DR. LITMAN: Thank you. Dr. Mehta?

DR. MEHTA: Hi. Reema Mehta. I wanted to echo some of the comments that were just made regarding the public health impact of this and some of the other comments that were made regarding some of the safety concerns of the individual

components. I think we need to first acknowledge that FDA has already determined that there is a favorable benefit-risk profile for celecoxib, as well as tramadol. So some of this applies across the ingredient and is not unique to CTC, and there's nothing about CTC that suggests that there would be a different profile as it relates to some of those matters.

Also, I wanted to echo the comment about tramadol light, specifically with regards to public health. I think in this case, we're talking about less is more. So having the opportunity to be able to leverage the benefits of tramadol at a much lower concentration I think is something that should be valued here. We see that as evidenced by a lower Tmax and a lower Cmax while sustaining efficacy through the clinical trials.

I think also having that lower concentration of tramadol may be an innate property of being abuse deterrent as compared to single-ingredient tramadol, where you will get a more pure exposure to tramadol as well as have higher concentrations

as compared to this product. Thank you.

DR. LITMAN: Thank you. Dr. Suarez?

DR. SUAREZ-ALMAZOR: Yes. I would like, if it's possible, to show the sponsor's slide 51.

DR. LITMAN: Fifty-one.

DR. SUAREZ-ALMAZOR: Thank you. Though this relates to efficacy, at the end of the day what we have here is a negative trial with a drug that doesn't seem to be better than using celecoxib alone. All three compounds were better than placebo, but there were no differences between them. From a public health perspective, we are talking about adding another opioid compound that hasn't really shown better efficacy than even the single ingredients, and we don't have a comparator with the single ingredients used together.

DR. LITMAN: Thank you. Dr. Sullivan?

DR. SULLIVAN: This is timely to follow on that because I think I've heard two different things, and I don't know if people can help clarify that slide 50 showed p-values comparing the change in SPID for tramadol versus CTC and shows a

significant difference. I think confidence intervals on slide 51 appear to overlap here. They're showing a significant p-value, and I think if this is an important consideration, we should try and resolve that, our understanding of that.

DR. PLATA-SALAMAN: Can I clarify, please?

DR. LITMAN: Sure, Dr. Plata.

DR. PLATA-SALAMAN: Slide 50, please, CO-50. This is the primary endpoint according to the clinical protocol and the request by the FDA. Yes, you'll see a significantly better efficacy of CTC compared to tramadol, to celecoxib, and placebo. The statistical significance is at the bottom. Those are the compilations related to the overall data in the SPID 48. If you look into the confidence intervals, the CTC has minimal or no confidence intervals overlap with the other groups.

Slide 51 is a different analysis. This is intended to show that if you subtract the placebo effect, which is very typical of these trials, you get an almost doubling effect in the SPID 48 of CTC compared to tramadol and celecoxib. In this

analysis, also there is clarity as it relates to the SPID in general. Slide 50 is one that it is used for supporting the approval of this product, which is based on the clinical protocol and statistical plan.

DR. LITMAN: Dr. Sullivan, was that the answer?

DR. SULLIVAN: Yes. I just want to clarify that the slide 50 analysis was -- I'm checking clinical trials.gov, but that was your prespecified --

DR. PLATA-SALAMAN: Yes.

DR. SULLIVAN: -- for efficacy.

DR. PLATA-SALAMAN: This was our prespecified analysis on this, and we fully agree also with the different sensitivity analysis that the FDA conducted and additional analysis that we did. The conclusion of all the different analyses is that CTC in the different sensitivity analysis, too, is significantly better to tramadol, to celecoxib, and placebo.

DR. LITMAN: Thank you. Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. I see a lot to like about this combination drug. Many people have said positive things about the lower amount of tramadol being used, but I am concerned how we can approve an opioid, even at a lower dose, in a combination that has a history of abuse and misuse without having a clear picture on HAP studies or what would really happen if this was abused. That's as fast as I can talk.

DR. LITMAN: Thank you. Dr. Higgins?

DR. HIGGINS: I have several concerns related to the abuse potential and the potential impact on public health. I guess my first point, and what I'm a little concerned about, is the fixed-dose combination product, which does not really allow for titration or dosing at different amounts and flexibilities. I'm also concerned about the fact that there's no excipients to deter abuse or resist manipulation of the product. I was drawn by the FDA's data regarding the tramadol-involved overdose deaths increasing between 2011 and 2017.

Perhaps one of the most important points I'd like to make, which was raised by the first public speaker, was the financial cost of introducing a new product that is arguably, perhaps, not superior to other products that exist, and what kind of financial impact that would have on the public is also something I'd be concerned about.

DR. LITMAN: Thank you. Dr. Meisel?

DR. MEISEL: Steve Meisel. I agree in some ways of looking at this, this is tramadol light. But there's one thing that hasn't been articulated real well, and that is this is a different chemical molecule, if you will, this crystal. So what would happen if somebody were to go and inject this stuff and now we've got this crystalline combination chemical, large molecule? What happens when that's in the bloodstream? Does it precipitate? Does it get into the lungs, does it get into the heart, does it get into the kidney, does it get someplace and cause all sorts of nasty things that otherwise would be unpredicted by the individual ingredients alone.

We've had experiences with excipients that have later come back and haunted us, and products have had to be taken off the market for that reason. There's no new chemical here. It's a different way of producing these molecules, but does that combination, that way of producing these molecules, create some risks that have not been explored at all?

We have no idea whether there is a risk or there isn't a risk, and from a public health point of view, we run the risk -- overusing the word risk -- of introducing some problems that are otherwise unpredictable for benefit that I think we all would agree is light in terms of clinical value.

DR. LITMAN: Dr. McCann?

DR. McCANN: I had the identical comment. This is a crystal. Presumably it dissolves slower in the acidic environment of the stomach. I would like the sponsor to answer whether there is any evidence that when it hits the bloodstream it dissolves immediately or does it turn into

microemboli as Dr. Meisel was talking about. Thank you.

DR. PLATA-SALAMAN: Can I clarify?

DR. LITMAN: Dr. Plata, please?

DR. PLATA-SALAMAN: Yes. CTC fulfills the requirements of immediate release, so it dissolves 85 percent within 15 minutes in vitro. When the tablet is taken, it is dissolved in the gastrointestinal system. When it's already in the blood, it's only the two individual components.

DR. McCANN: What if somebody injects it?

DR. PLATA-SALAMAN: It will dissolve into its two components.

DR. MEISEL: How quickly?

DR. PLATA-SALAMAN: We don't have the data to answer this question.

DR. LITMAN: Dr. Marshall?

DR. MARSHALL: Brandon Marshall. Thinking about these public health impacts are challenging because of the hypotheticals here, but I think one hypothetical that I'm struggling with a little bit is the extent to which you may see expansion versus

replacements.

So I'd be interested in hearing from clinical panel members whether this product is likely to replace hydrocodone products or whether you might actually see expansion of patients exposed to opioids and whether this would be used instead of non-opioid options. I'd have much fewer concerns if the anticipated impacting clinical practice is the former; that is that this substance will simply start replacing hydrocodones, oxycodones, and so forth.

DR. LITMAN: Sure. Dr. Michna?

DR. MICHNA: Well, the problem is we don't have the data, right? They haven't done this study. This is approved for acute pain. It's only for postoperative pain for 48 hours, which is my problem. I think initially what's going to happen is you're going to get an oxycodone script, you're going to get this, you're going to get something else because nobody wants the phone calls. And I think this just complicates things, and patients are confused, and there's nothing to stop them from

taking two of these and not getting anything, and then taking oxycodone, and at that point be oversedated because they've taken so much stuff.

I wish we had more realistic clinical studies that would show us how this would actually play out. Right now, I'm very concerned about this breakthrough issue, and it's not been adequately explained to me what's going to happen.

DR. LITMAN: Dr. Zaafran?

DR. ZAAFRAN: Thank you. Let me try to bring this back to the clinical setting because I think that's what --

DR. LITMAN: Is it public health related?

DR. ZAAFRAN: Yes, absolutely. From the standpoint of what we do in a practical setting from how we prescribe today, we prescribe opioids for short term and we prescribe, or we try to prescribe, nonsteroidals and other medications to kind of supplement it in a multimodal fashion. From my standpoint, medication, the way it's structured right now, will probably decrease the way we prescribe opioids in a short-acting fashion

from the standpoint of trying to cover for the breakthrough. So from that standpoint, I think it's actually going to be safer from a public health standpoint.

The way we have a lot of states right now, they limit the number of days that acute pain medications can be prescribed, either 7 days or 10 days, depending on which state it is. So the medication as it's going to be prescribed is going to be limited to those number of days as the states prescribing to. With the PDMP that we have to check in many states also, we're going to be looking for physicians prescribing oxycodone along with this, along with something else, because it's something that we are encouraging folks not to do.

So the way I practically see this happening right now is that as opposed to the intraoperative/perioperative setting, a physician prescribing things in a multimodal fashion, and as soon as they get discharged, the surgeon does the easy thing of I'm going to just give Vicodin or Percocet and maybe you can take a nonsteroidal on

the side; here you have a q-12 dosing of both, an opioid and a nonsteroidal, which is more practical from the standpoint of what we need, and they can take acetaminophen in addition to that if they need it for breakthrough pain.

From the clinical standpoint, I think it's better for public health and I think it's more practical for the clinicians who are trying to manage acute pain postoperatively.

DR. LITMAN: Thank you. Just a reminder to speakers to state your name for the record.

DR. ZAAFRAN: Sherif Zaafran.

(Laughter.)

DR. LITMAN: Dr. Sandbrink?

DR. SANDBRINK: I'm not going to comment anymore --

DR. LITMAN: State -- sorry -- your name.

DR. SANDBRINK: Friedhelm Sandbrink. I don't want to comment too much about the need to actually have an injection study and experiment to some degree because of the crystallized structure that was mentioned, but mostly to the public health

concern, we have to realize that people will look at this, if approved, and we'll start making modifications based on assumptions that they make.

So on one hand, I'm quite bothered that we don't actually have a comparison in a clinical study that compares this with both active ingredients taken together. We have a comparison with tramadol; we compare with celecoxib. I do understand that there are reasons in regard to the blunted effect of celecoxib taken together with tramadol if it's not in a crystallized form, but the reality is people will look at this and they will start using tramadol and celecoxib possibly together from the generics that are out there or from the pure medications that are out there. So that's a public health concern, and not having a comparison is quite bothersome to me.

On the other hand, if I look at -- also, I fear that there's an expansion in regard to actually using tramadol. It's blunted effect, as we heard, in regard to the initial release, but after 6 hours, despite having a reduced Cmax and a

prolonged Tmax, after 6 hours, the plasma level is the same as if I gave tramadol alone.

So I suspect still, despite everything that we've seen, that the effect after 6 to 12 hours is really the celecoxib effect, and the SPID doesn't address that because it's a combined 48-hour summary score. So I fear that we may be exposing patients, who could be very well treated with celecoxib alone, to a combination with tramadol as low as the dosage is, because if they get benefit from this throughout the 12 hours, probably it's a nonsteroid towards the end of it.

DR. LITMAN: Thank you. Dr. Goudra?

DR. GOUDRA: Oh -- none [indiscernible].

DR. LITMAN: Dr. Amirshahi?

DR. AMIRSHAHI: Maryann Amirshahi. One of my concerns is I think the landscape of tramadol prescribing and abuse is really evolving, so if we look at recent prescribing and overdose trends, there have been studies that have shown that there's been an exponential uptake in tramadol prescribing, and the studies that were presented

obviously showed that.

So I'm concerned because, number one, I think we do know that it's probably safer to prescribe tramadol than oxycodone, but the issue is, are we going to see a much larger uptake in the tramadol prescribing because there's this perception that it's safer but it's not completely safe. I think that's kind of what got us into the problem with the opioid epidemic in the first place.

As Dr. Hoffer, I believe, said, a lot of his patients started with a prescription opioid. They didn't start with heroin, the vast majority of them. So the concern is that if we have something that we think is safe and we're prescribing it like water, how is that going to change the rates of tramadol abuse?

For example, is that an introduction to other opioids? Because as an addiction medicine practitioner, I also find that a lot of people didn't start with heroin or oxycodone, and something that was perceived to be safer was what

actually got them started on the path to opioid addiction.

DR. LITMAN: Dr. Hoffer, did you still have a point?

DR. HOFFER: I think the data shows that it was oxy that got people started to move to heroin. I appreciate that low-dose opiates are dangerous. I think all opiates are dangerous, and I think there's a linear relationship in their danger and how potent they are. For me at least, if we're going to have an opiate on the market that's being used for acute pain in these circumstances, I'd like it to be one that has the lowest MME possible.

I don't want any opiates prescribed. That's the ideal. No opiate prescription is the best way to avoid any complications associated with opiates, but that's just simply not what happens. So I think here, whether it's a replacement for tramadol -- and maybe there are some other effects with the Celebrex, but I think that it's so low that I'm not sure this committee would approve -- or the FDA would approve any opiate

medication. What if it's 2 MME; is that acceptable? It's still going to pose some risks.

So I think it's the relative risk that I think is important to me. I don't want people on Percocet or Vicodin, or even Ultram, if they can be on something that has less opiate medications, an active ingredient, is all I'm saying. And I do think that people do progress. They progress to higher doses of opiates. That's how you have tolerance to these drugs, and there are some withdrawal symptoms associated with them. But as you go up in MME, those things get much greater and are much more motivating as far as using the escalating doses, and abusing, and misusing drugs.

DR. LITMAN: Thanks. I'm going to have to stop there in the interest of time. I just want to try and sum up what are a lot of very divergent views.

On one hand, I heard some of the pros, meaning the good aspects of the public health uses of this drug, meaning that it's better than existing, than what's out there, and there are

relatively lower rates of abuse. But on the other hand, I heard some panelist members that were concerned about the potential for IV abuse, concerned about what do we do about rescue medications in the postoperative acute pain setting; polymorphisms that could impact either those patients that may not get enough relief, or on the opposite end of the spectrum may have a relative overdose without realizing it.

I heard some concerns about maybe the recognition that these two drugs might be beneficial together could lead people to using the generic products separately more often than not. Then finally, although it's not the specific purview of the FDA that was mentioned, we all know that when a combination drug goes on the market, it's vastly more expensive than the two generic drugs alone.

Again, I apologize. We're kind of tough on time today because we have another meeting this afternoon, and we need to really end the vote by 12:30. So I'd like to go to the next question.

Discuss whether the benefits outweigh the risks for the proposed indication and discuss if any additional data are needed for this application to be approved. Again, I ask the committee to state your name first and keep your answers short without a lot of circumlocution. I've been waiting to use that word, by the way.

MALE VOICE: Can you say that again?

(Laughter.)

DR. LITMAN: Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. My interpretation of the data presented are that there really is no indication that CTC has a substantial advantage over any other approved analgesics on the market. I'm also concerned about the special populations and would like to see some additional data analysis on those, meaning the people who have preexisting conditions of mental health concerns or substance-use disorders.

DR. LITMAN: Dr. Meisel?

DR. MEISEL: Steve Meisel. We talked about some of the risks before. I go back to the fact

that this drug isn't all that terribly effective. I look at FDA table 7, in the FDA briefing packet, any rescue medication, anytime, 76 percent, and that compares to 83 percent for tramadol and 88 percent for Celebrex; within the first 4 hours, 49, 61, 65. I mean, it's a little better but not a whole lot. So that tells me that you need breakthrough pain relief of some type, and it's going to be Tylenol, it's going to be oxycodone, it's going to be something, and then you end up with added risks associated with that.

The fact that we don't have a comparator trial of this drug versus the two ingredients separately combined, as individual ingredients combined, to me is a flag. I can't say this is more effective or less effective than just giving tramadol and celecoxib in individualized doses, in full doses, and see what happens. To me, that would be the data that we would need in order to satisfy any question that this drug is actually effective.

DR. LITMAN: Thank you. Dr. Goudra?

DR. GOUDRA: Basavana Goudra. I was going to repeat what Dr. Meisel said; unless you do one more studies where you try both tramadol and celecoxib on their own and prove that it works better than just celecoxib alone or tramadol alone, yes, it's going to be tough.

DR. LITMAN: Dr. Hernandez-Diaz, please?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I was trying to put the pros and cons as you were doing. In the pros, I have a slightly different reading of the evidence presented, which I think shows comparison with active ingredients within the component, and I particularly like that part of the trials. The sponsor included super doses.

I like the idea of the combination because the average efficacy in the population, where there might be some response to opioids and some to NSAIDs, is kind of covert [indiscernible], so I think it is fair game that some patients will be responding to the celecoxib part and some to the opioid. We know that not all patients will respond to any opioid, and by doing so, they may be less

likely to keep increasing doses of opioids.

I also like the fewer pills if patients need both and the practicality benefits that go with that. From the safety point of view, I think the delayed tramadol and how it might deter abuse -- the lower doses that are needed may deter abuse, and maybe the added NSAIDs and the crystal, the complications of abusing might also reduce abuse.

I also liked the emphasis on the acute indication versus the long-term claims for the use of opioids. That increases the efficacy because we see not perfect but more efficacy with acute use. It also reduces, as indicated, the safety concerns including for the COX-2; the time is going to be lower in any case. I think that makes it a good alternative to Schedule II opioids overall, and oxycodone in particular, not only to tramadol alone.

Finally, in terms of pros, I see that the two components are approved already with the contraindications and with the birth defects that

are known. So I think the combination, by lowering doses, if anything, it has been shown to improve it. But of course in the cons, we have the opioids, and with the opioids, doing bad things with them and increasing the doses, we are always going to probably have concerns of the use and misuse.

So the way I'm looking at that is if we can have utilization of these new products as a replacement of things like oxycodone or for Schedule II, then it will be a benefit. If it is an added use, then it will not. I cannot predict the future, but that's the way I was looking at it, is maybe we can use it as a replacement. And finally, in terms of the concerns, there are concerns that have been raised about the combination and if the crystal is going to create any additional problems.

DR. LITMAN: Thank you. Dr. Block?

DR. BLOCK: Yes. This is Laura Block. A while back, we lost Darvocet, which was one of the shallow end of the pool sort of opiates for

moderate pain. This could be something that would go very nicely in that open spot, but we would want to get data about the solubility and maybe some animal studies for IV use.

DR. LITMAN: Thank you. Dr. Garcia?

DR. GARCIA-BUNUEL: I'm going to be really brief and not comment because --

DR. LITMAN: Just say your name first; sorry.

DR. GARCIA-BUNUEL: -- they've been repeated. Martin Garcia-Bunuel. Points have been made.

DR. LITMAN: Thank you. Dr. Setoguchi Iwata.

DR. SETOGUCHI: Soko Setoguchi. To me, since the individual medication is already available on the market, the real benefit of this drug has to do with the co-crystal and then has to be compared to the two individual drugs taking together, either showing less side effects or more effectiveness. So to me, the benefit is not really proven in the trial.

In terms of the risks, I don't think the combination drug would pose more risk than the individual drugs taken together based on the data presented. At the same time, though, on the public health side, the sort of unknown aspect of these crystals, I think at least in animal models or in vitro, when injected as an IV drug, that might have to be proven at least safe or not, behaving unexpectedly.

DR. LITMAN: Thank you. Dr. Shoben?

DR. SHOBEN: I just wanted to say that I actually think the benefits of this drug have been pretty well shown in the clinical trial data, and the concern about not looking at the co-crystal versus the two drugs taken together, while it would have been nice, the pharmacokinetic data really suggests that there's no reason to expect a difference, and the two together would give you that much of an effect. In fact, the celecoxib pharmacokinetic data when taken together with tramadol was a lot lower, so you would expect less pain management from the two taken together.

So between the pharmacokinetic data and the clinical trial data showing the superiority of the co-crystal versus tramadol alone, versus celecoxib alone, I think the benefit is pretty clear.

DR. LITMAN: Dr. Horrow?

DR. HORROW: Jay Horrow. I think that the data shown in slide 50 from the sponsor's group shows very unmistakably that a single phase 3 study has been sufficient. The p-values are less than 0.001, and that is well within the criteria for a single phase 3 study. I agree with Dr. Shoben that the data regarding dissolution are very clear and show that a comparator group of tramadol and celecoxib is neither necessary nor insightful in order to provide clear inference on efficacy. The q-12 hour dosing is better than q-6 hour dosing of tramadol. This would be a benefit for patients.

DR. SUAREZ-ALMAZOR: Thank you. Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. I would be interested in knowing more about the withdrawal issues, and if there's a need for titration, how

that would be handled. The breakthrough pain continues to be a big issue with me, how it's handled. The abuse and misuse effects, we don't know what we don't know. While I think that efficacy has been shown, I really would like to see a study comparing the combination of tramadol and celecoxib with CTC as a head to head.

DR. LITMAN: Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff. I would just like to say, from the benefits outweighing the risks perspective, being that these are two drugs that have been available for a number of years, that the ability to consider a Schedule IV medication at a lower dose in my mind makes the benefits outweigh the risks. Thank you.

DR. LITMAN: Dr. McAuliffe?

DR. McAULIFFE: I'm sort of drawn to the idea of the low MME and that's very appealing, but the other part of me is sort of torn. It takes away the patient's choice, really, to decide whether they want to use tramadol or not. They have tramadol and celecoxib. I think that if it

was a tramadol single entity that they had the choice of using with the nonsteroidal, they might take a half dose, they might take 25 milligrams, and they may even take less than that. So I think that making it less flexible for patients may encourage them to use an opioid where otherwise it may not.

DR. LITMAN: Dr. Marshall?

DR. MARSHALL: Brandon Marshall. I agree with many of the benefits that Dr. Hernandez-Diaz stated, but one additional benefit, I think, that hasn't been discussed much is presented on slide 54 of the sponsor. I do see the high rate of rescue medication is something to consider, but when you look at the opioid, the oxycodone rescue medication, it was significantly lower in the CTC group. I'm assuming those Kaplan-Meier curves are significantly different, but I think that is a benefit, that we see less utilization of oxycodone in the CTC group as a rescue medication.

Regarding the risks, I really do feel like the risks of injection of this substance are low,

and this is from someone who's been involved in long-standing cohorts of people who inject drugs. Reflecting on what Dr. Hoffer said, I just don't see this as going to be injected very frequently, and that's shown in the NAVIPPRO and RADARS system. Now, it probably can and will happen, but I think that's going to be not very common.

DR. LITMAN: Dr. Sullivan?

DR. SULLIVAN: I just want --

DR. LITMAN: State your name into the record; sorry.

DR. SULLIVAN: -- Patrick Sullivan. I think there's been some discussion about efficacy, and I also just want to say that I rely on the primary endpoint analysis that I think demonstrates the CTC as being superior to tramadol and celecoxib. In terms of the public health benefit, just the idea that it is a lower dose, that more pain relief is available with lower tramadol plasma concentration, seems to me to be lowering the cumulative burden in exposure. I'm also motivated by the lower use of opioid rescue medications. I also weigh this as

the benefits outweighing the risks.

DR. LITMAN: Professor Phillips?

MS. SHAW PHILLIPS: Marjorie Shaw Phillips. The real unanswered question as far as comparisons is CTC versus full-dose celecoxib. The celecoxib was not dosed optimally with a loading dose.

DR. LITMAN: Thank you. Dr. Zeltzer?

DR. ZELTZER: I guess one public health risk that hasn't been addressed is just as other combinations in the past, Tylenol with codeine, ended up being used for chronic pain in a subpopulation, we don't have any longitudinal data besides the 48 hours. From a public health standpoint, if this is available, will it be used chronically for people with chronic pain? Because as a new combo drug, it's seen as safer in higher doses than what was recommended. So I still see it as a potential public health risk and, again, a difference in metabolism between celecoxib and tramadol.

DR. LITMAN: Thank you. Dr. Setoguchi Iwata.

(Laughter.)

DR. SETOGUCHI: Soko Setoguchi. I have two last names like Sonia. I just want to echo and also follow up that the fact that this is a combination drug makes us prescribers difficult to drop one drug component. If we started celecoxib and then tramadol at the same time, if it's a separate drug, it's easier to drop one once the patient's pain is controlled. But that's also another concern that it might encourage continuous use of both drugs, including tramadol, and may increase more of an addiction population.

DR. LITMAN: Thank you. I think that's it. I'll just add my own two cents here at the end. Over the years, I've seen a pretty substantial decrease in the amount of opioids that my surgeons have prescribed, my personal practices in anesthesia, and I work with my surgeons pretty closely. Although it's mostly children, there are an awful lot of teenagers, too, so they've really been limiting it.

Other than the usual combination of Tylenol

with oxycodone or hydrocodone, my surgeons don't really prescribe any kind of combination medicines, and if I ask them what do you think about tramadol or celecoxib, they would be like, "What are those?" So I can't imagine them ever adopting this medication if it were approved unless they had a lot more efficacy data that's published in their literature. I also fear that if it's perceived as a less, or morphing light, or whatever you want to call it, a less abusive or a less potent opioid, that they might be more likely to prescribe it in opposition to just not giving opioids at all.

On the other hand, there are so many advantages here that we've already talked about, so I'm just going to try and sum up the discussion here. Again, I've heard a lot on both sides. The pros were that it's a better alternative than the usual with lower MMEs and less abuse potential; that the phase 3 study was sufficient; that the q-12 and the combination would be more convenient for patients; and that the overall benefits outweigh the overall risks.

But on the other side, I heard that there was no evidence of clear advantages in introducing another kind of opioid into the market. There were not different populations studied well enough; that the phase 3 trial was missing the ultimate comparator, which is the two drugs in combination by themselves. I'm not sure if that makes sense, but both the tramadol and the celecoxib given together, just not in this particular CTC preparation.

Did I get everybody's -- did I sum that up correctly?

(No audible response.)

DR. LITMAN: Great. Now we're going to head over to the votes. We will be using the electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or if you wish to change your vote, you may press the corresponding button until the vote

is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO, Moon, will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed.

I guess there's just only one voting question; is that correct? The one voting question we have before us is do you recommend the FDA approval of tramadol 44 milligrams and celecoxib 56-milligram tablets for the proposed indication in the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate?

This is different from yesterday. Thank you.

(Laughter.)

DR. LITMAN: Yes, no, or abstain.

(Voting.)

DR. LITMAN: I'm told that the votes are in, and they'll appear on the screen. Everyone has voted. The vote is now complete.

(Laughter.)

DR. CHOI: For the record, we have 13 yes, 13 no, and zero abstentions.

DR. LITMAN: Now that that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, you could state the reason why you voted as you did into the record. Please be cognizant that I will have to adjourn by 12:30.

Who is first? I guess that's Professor Phillips.

MS. SHAW PHILLIPS: Marjorie Shaw Phillips. The vote reflects the way I feel about this, half empty versus half full. I voted yes because I see a benefit over what is happening now for the people that now are getting the two sole ingredients with the interaction being less effective therapy, and

the potential advantage of the co-crystal with optimal dosing like scheduled acetaminophen being better than what's happening right now. I do have concerns about IV drug abuse and overuse of this product.

DR. GARCIA-BUNUEL: Martin Garcia-Bunuel. I voted yes. In all fairness, I think the data presented for its proposed use did just that; I understand maybe not as robust as some would like. I see the potential for it in the practice settings that I'm familiar with, potentially replacing use of some other short-acting opioids.

My only qualifying statement, and I'll try to keep it short, would be that I do think we have to be cognizant of the potential, or not just the potential but the reality that this medication will sneak out of the perioperative setting. It will enter the emergency department, primary care settings, and other ambulatory care settings.

I have some confidence. As Dr. Zaafran has commented, I think we are in a better place for monitoring and oversight of prescribing practices

within medical staffs, medical systems, and states, but having said that, there will have to be diligence. Then finally, I think if we can be informed in the future more about the potential for abuse and risks related to unintended long-term use, we need that partnership from industry to really take that seriously. Thank you.

DR. GREEN: Traci Green. I voted yes. I felt that the data that were presented indicated a greater benefit with this drug than with the component APIs and that there was greater risk of the component APIs on their own, especially with respect to abuse and misuse. I think the public burden for tramadol per prescription, even though we are seeing rising increases in prescribing of tramadol, in circulation, we see lower emergency department visits and fewer deaths associated with this particular molecule.

I think we can anticipate an even lower rate with this product given the lower API and the lower MME. Drug liking from other human abuse potential studies of tramadol indicate that it's the least

liked opioid, and the postmarketing surveillance data have for many, many years shown that it has very low rates of misuse and nonmedical use, including injection as a route of administration.

I spend most of my time working with people who use drugs and people injecting, and this is not very interesting postmarketing surveillance, and studies would be really helpful, I think, on the molecule, but it does look like something that could be helpful, identified, and designed in a postmarketing environment and should be done for public health.

DR. HOFFER: This is Lee Hoffer. I voted yes for the reasons that have already been stated, primarily. But I do want to say that I think this medication does pose risks like all opiate medications. I just think in this particular indication it's as about a low amount of opiate medication that you can have in a medication.

DR. MICHNA: Ed Michna. I voted no, and it was purely based on the fact there's not much flexibility with this drug. My concern of what to

do for those patients that are going to have breakthrough pain with this, there's no clarity on how to approach it other than the study itself, which was oxycodone, and that's not going to help us by giving patients both these drugs.

DR. SETOGUCHI: Soko Setoguchi. I voted no. I think I already mentioned the reason, that I don't think the trial reflected the real-world use of a medication where already the individual drugs are available on the market. Whether or not to use a combination using each individual versus this combo, a benefit should be proven against the two drugs taken together.

DR. McCANN: Mary Ellen McCann. I voted no. My concern is although the abuse potential may be lower than other narcotics, there will be people that will abuse this, and we have absolutely no information about what happens to those people if they do inject this drug. We actually don't even know if it's injectable. So that's why I voted no.

DR. ZACHAROFF: Kevin Zacharoff. I voted yes, and from my personal perspective, I'd like to

congratulate the sponsors on their presentation. I think it was a very comprehensive presentation and made a good case for me about how a Schedule IV medication could be combined with non-opioid medications to provide adequate relief.

I do fully expect that this will be used in settings other than postoperative pain management, which in my mind is actually a good thing. I think philosophically, sitting on this committee, if we take into account the fact that Schedule IV means what it means with respect to abuse and misuse, we may be very nervous about abusing future Schedule II medications in the absence of data. But if somebody brings to us a situation where we have an opioid-sparing formulation of a Schedule IV medication, in 2020, this is as good as it gets for me. Thank you.

DR. McAULIFFE: Maura McAuliffe. I voted no mostly because we've heard that tramadol is the second most dispensed opioid in the United States. It is abused and misused mostly orally. There's concern that this drug would be misused in that way

as well. Forty percent of the misused tramadol is the multiple entity product as this would be, so I think we could plan on this actually taking the place of the most abused tramadol that's out there. It is a lower MME, and I think that that is appealing as I said, but I think that takes away choices for patients in a lot of ways. So for me, no.

DR. ZELTZER: Hi. Lonnie Zeltzer. I voted no more for the public health hazard. Besides what was mentioned about not knowing IV toxicity, my worry is that as a new combo drug, it will be seen as low addictive because of misunderstanding of Schedule IV, and it will end up being used by the public for chronic pain. We don't know about the long-term effects of the combination, especially in special populations, the elderly and those with CVAs on baby aspirin and on SSNRIs, just all the potential risks for its chronic use. So I would like to see a little more testing in other populations first.

DR. GOUDRA: Basavana Goudra. I voted no

because I really want to see a head-to-head comparison as I mentioned during the discussion.

DR. LITMAN: Ron Litman. I voted yes. I don't envy your discussions. Sorry guys, but overall I just felt that the benefits outweigh the risks. As I mentioned before, I predict -- and I'm not very good at predictions -- this will not be very useful in the immediate postoperative period. It takes too long and it may be too weak. I agree with Dr. Michna that there's going to have to be some rescues, and once my surgeons figure that out, they're just going to stop prescribing it.

I don't think that the risks outweigh the ability of the company to put it out into the marketplace and let doctors choose for themselves whether or not to study it further for their patients. I think there's been a lot of publicity about the cost of combination medications in comparison to the generics, and you know what, the insurance companies are going to have to figure that out and cover it if they think it's worth it. So overall, I just thought the benefits outweighed

the risks.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted yes as an alternative to opioids in a Schedule II and not to alternative treatments that should be the first line. I think the vote reflects -- between person balance, so sorry about that.

DR. SHOBEN: Abby Shoben. I voted yes. I talked about the benefits earlier. I stand by that. I think the remaining concern I have is about what Dr. Marshall talked about, which is this product going to be a replacement for existing Schedule II opioids that are prescribed in this acute pain setting or is it going to expand the market and give opioids to patients who are not currently getting them? I think that's something to look at postmarketing.

DR. MEISEL: Steve Meisel. I voted no. We've already talked about the lack of data about abuse if it was injected and what new risks might be imposed there. We need to have that data before I'd feel comfortable approving this. The same is

true with the lack of any comparative data to the single ingredients. I think that's a baseline, but something that could be done by the sponsor, if they desire, relatively easily.

One other comment that we haven't talked about before that I think we need to be aware of is that this 56/44 ratio is not based on any clinical science or that that's the right ratio. It's based on the fact that that's the chemical properties to allow them to make this crystal. That's what's driving the ratio of the celecoxib versus tramadol, not anything clinical. Is that the right combination? Is that the right ratio? Who knows? We don't know that, but we're sort of locked into that based on the chemical properties.

All of that said, if the agency goes ahead and approves this, I think the risks become almost zero because although it's beyond the scope of what the FDA needs to consider here, I can't think of a single third-party payer, insurance company, or hospital that's going to put this product in their formulary. This will be paid only out of pocket,

and out-of-pocket costs for drugs, with insurance going the way it is, it's just not going to be tenable. No third-party payer, no PBM, no hospital's going to put this on their formulary when they have the individual ingredients, particularly in the absence of any data to show that this is superior to using those drugs as individual ingredients combined.

DR. HIGGINS: Jennifer Higgins. I voted no for the reasons that I stated previously.

MS. ROBOTTI: Hi. Suzanne Robotti. I voted no, reluctantly. If this was going to be prescribed to me tomorrow, I would use it. I would be in favor of using it. But I cannot rush to approval because in looking at the totality of the public health issues and the clinical questions that just are not answered -- how to handle breakthrough pain, titration, the lack of IV abuse, risk, and the lack of information on the long-term effects -- could all cause a public risk and a burden that I'm unwilling to vote for. I'd also like to see acetaminophen tested as a rescue drug.

DR. BLOCK: This is Laura Block. I voted yes. I believe there is a need for it in the box of tools that we use for pain, and I believe that coming out of the postoperative setting, patients could be loaded as they wake up with something such as maybe IV Tylenol, or a nonsteroidal, or even just a single dose of an opiate, then that way they get this and have smooth sailing, and they go home. Thank you.

DR. AMIRSHAHI: Maryann Amirshahi. I voted no. The reason that I voted no was I didn't feel that the comparisons were appropriate with regard to the celecoxib dosing, as well as the lack of combination. I don't think that they really demonstrated a benefit over what is on the market with a concern for increased costs. I do feel that it is less risk for abuse than a lot of the other products that we have out there, but I'm worried that we would have a false sense of security with regard to that it's safe but there is still a risk; then finally, the lack of titratability that you have with individual agents. Thank you.

DR. PISARIK: My name is Paul Pisarik, and I voted yes, more for the fact that maybe this might take the place of Schedule II narcotics, and therefore be less risk.

DR. SANDBRINK: I'm Friedhelm Sandbrink. I was very much split. I voted no, but like this, I felt very much split about this. I think what swayed me towards the no was the lack of comparators that we talked about, but also in particular, a comparator to a higher dose nonsteroid such as celecoxib for the immediate postoperative period because that is, I think, a relevant comparison clinically. In regard to the public health concerns, I think it's a wash, so I think we cannot predict that.

DR. ZAAFRAN: Sherif Zaafran. I voted yes. I always hear that there's a lot of concerns about long-term use. Again, as a regulator, one of the things that we have been focusing on is making sure that physicians are prescribing things appropriately. So where folks used to prescribe medications for 30 days and with 6 refills, we hold

those folks accountable either by state law where they're not allowed to do that anymore, or if they are allowed to, if they're brought before regulators, we tell them that this is outside the standard of care.

From the standpoint of looking at an opioid, any opioid is going to have a potential for abuse, but if you limit the way it's prescribed to where it needs to be prescribed appropriately, in an acute postoperative setting, then this is a safer alternative for the Schedule II drugs that are out there.

As was mentioned earlier, if you are going to prevent patients from actually having pain before you start utilizing the medication, you're probably not going to use the rescue medication as much as you need. Right now, we have medications prior to surgery and immediately afterwards, so you have the nerve blocks that are working, and kicking in, and so forth, so you're not waiting until they have a score of 8 before you're actually medicating these folks. So I see less of a need for rescue

medication as much as folks actually think there would be, so I think there's actually a little bit less of a public health risk with this.

DR. SUAREZ-ALMAZOR: Maria Suarez-Almazor. I voted no. Celecoxib and tramadol are already on the market, and they are available for providers that may want to use both drugs. I think that there was not enough evidence to show that the compound is better with respect to pain, efficacy, or as a deterrent for abuse than both independent drugs used together.

I see the benefits primarily and convenience of taking one pill instead of two pills, but those were not enough in my view for a positive risk-benefit ratio, as I am concerned primarily about two things. One is the lack of data on IV use if this drug were to be misused and abused in that way, and the other one is the concern of using high doses of NSAIDs, of celecoxib, if this drug were used at a higher dose than recommended, especially in susceptible populations.

DR. SULLIVAN: Patrick Sullivan. I voted

yes, and I was primarily persuaded by the possibility of having opioid sparing and a lower cumulative dose if this replaces Schedule II options. I really respect the perspectives of different providers, some of whom felt like there are ways to manage this so it is used in that way and some of whom felt like it might not be.

I also just want to emphasize that when we talk about the comparison with the two components, this is a different formulation. The co-crystal, to me, was demonstrated to have some different PK advantages that would not accrue to using the two things separately.

DR. MARSHALL: Brandon Marshall. I voted yes for many of the reasons that have been described. I agree with the comment about the interesting pharmacokinetic profile. I feel, overall, this represents an incremental but important approach to addressing the opioid crisis in the United States, particularly if the medication were used in replacement of Schedule II opioids, which I did hear some support from

clinical panel members, although that was not consistent. But, overall, I feel like the benefits outweigh the risks.

DR. TYLER: This is Linda Tyler, and I voted no. I too want to compliment the company on the clarity of their presentation of data. As we all know, presenting data is challenging. I found their study credible. I agree with Abby that it didn't make sense to study the combination together based on their earlier trials. I believe in the trial what they showed is that they were able to decrease the dose of tramadol that was used, decrease the oxycodone rescue, and there was a delay in the peak of the tramadol.

I'm very intrigued with the crystalline dosage form and would like to see more about it, but I am concerned about some other things. We should not be fooled that this is rated a Schedule IV. This is an opioid agonist, and it has other properties as well. As was so well articulated in the public comments, tramadol is a tough drug to use. It has some different side

effect profiles. It's different than many of the other opioids that we work with. It can be erratic in its response.

What we saw actually in their 201 trial is that tramadol alone was not a very good pain reliever; that together the combination was better. So I'm unclear if celecoxib, if used alone and especially if you are able to titrate doses, would look better than this dosage form that we're considering today.

I also have a concern that would have to be addressed at some point if the drug went forward around a patient safety issue. This drug is being labeled as 100 milligrams, but it's 100 milligrams of two different components. Well, we also have 100 milligrams of the celecoxib on the market; we have 100 milligrams of tramadol on the market. I think there are opportunities for confusion, opportunities for confusion in our electronic medical record systems.

As we look at the abuse potential, I feel like there are some unanswered questions there that

we'd want a little more information about, but I recognize that this is a huge challenge. We're in the landscape of an opioid crisis, so we're all very, very concerned about that. We're asking for data that we would not ordinarily ask for of this product, and the trends are not really elucidating, and don't really help us, and don't really help us since, but what we see is a decrease in oxycodone prescribing, which is a great trend, but what's not overlaid on all the charts that we saw is we also see an increase in heroin use in the United States. Tramadol is part of that mix of another compound that people are going to -- and you saw that increased percentage of what was being used.

So it's really hard to pick it out of the trends, but I'm really, really concerned for those reasons.

DR. LITMAN: Thank you. In the last minute and a half that we have, can I ask Dr. Horrow or Dr. Mehta, do you have any less than one minute comments even though you weren't voting?

DR. MEHTA: Thank you. I think one of the

points that maybe didn't come across through some of our conversation also is that this is a 505(b)(2) application, so some of the expectations for what the sponsor would need to demonstrate through a 505(b)(2) application are not one in the same with the 505(b)(1) application. I know that sounds a little technical.

From my perspective, I think that in this case, there is a favorable benefit-risk profile, and if there is interest by the committee members around more data regarding the potential risk with IV administration, I think that's something that could be achieved through a post-approval requirement if that's where FDA felt things were necessary.

DR. LITMAN: Jay, any last comment in 20 seconds?

DR. HORROW: Jay Horrow. I'll just underscore what Reema said because if you took the number of no votes that I heard that were based on the IV issue, and if the sponsor is then able to show dissolution data in various solvents to show

what the crystals did, it sounds to me like those no votes would become yes.

DR. LITMAN: Before we adjourn, Dr. Lowy?

DR. LOWY: Thank you. I think when we all saw the 13 yes and 13 no, we all heard some laughter in the room, and I think that that split vote really reflects the complexity of the issues here and the difficulty of the questions that are being brought before us. So to that end, we really thank the committee for your wide spectrum of input. It is extremely valuable to us as we continue to review this application, so thank you and enjoy your lunch.

Adjournment

DR. LITMAN: I'd like to congratulate the committee on finishing on time, and we kindly ask that all attendees dispose of any trash or recycling in the proper receptacles in the hallway and not leave any waste items on the floor or tables.

Panel members, please remember to take all personal belongings with you, as the room is

cleared. But that's not the end of the meeting day, so that's up to your discretion. We will now adjourn the meeting and meet back here in exactly one hour.

(Whereupon, at 12:30 p.m., the morning session was adjourned.)