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 SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

Wednesday, February 14, 2018

8:00 a.m. to 12:26 p.m.

FDA White Oak Campus

Building 31 Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

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. McCANN: Welcome and good morning. I would like to remind everyone to please silence their cell phones, their smartphones, and any devices if you have not already done so. I would also like to identify the FDA press contact, Michael Felberbaum. If you are present, please stand. Thank you.

My name is Mary Ellen McCann. I am the acting chairperson of the Anesthetic and Analgesic Drug Products Advisory Committee, and I will be chairing this meeting. I will now call the joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order. We will start by going around the table and introducing ourselves. We will start with the FDA to my left and go around the table.

DR. HERTZ: Good morning. I'm Sharon Hertz.

I'm the division director for the Division of Anesthesia, Analgesia, and Addiction Products.

DR. FIELDS: Hi. I'm Ellen Fields. I'm the deputy director in the same division

DR. STAFFA: Good morning. I'm Judy Staffa. I'm the associate director for public health initiatives in the Office of Surveillance and Epidemiology.

DR. McANINCH: Good morning. I'm Jana McAninch, also in the Office of Epidemiology.

DR. CHOUDHRY: Good morning. Niteesh Choudhry. I'm an internist at Brigham and Women's Hospital and professor at Harvard Medical School on DSaRM.

DR. RUHA: Hi. I'm Michelle Ruha. I'm a medical toxicologist at Banner University Medical Center in Phoenix and a clinical professor at the University of Arizona College of Medicine.

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

DR. SHOBEN: Hi. I'm Abby Shoben. I am in

the Division of Biostatistics at The Ohio State University.

DR. RAGHUNATHAN: Hi. My name is Trivellore Raghunathan. I am at the University of Michigan. I'm professor biostatistics, and I'm also director of the Survey Research Center at the Institute for Social Research.

DR. CRAIG: Good morning. David Craig. I'm a clinical pharmacist specialist at Moffitt Cancer Center in Tampa, Florida.

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

DR. LITMAN: Good morning, and since no one said it, Happy Valentine's Day. I'm Ron Litman. I'm a pediatric anesthesiologist at Children's Hospital Philadelphia and the medical director of the Institute for Safe Medication Practices.

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

DR. McCANN: Mary Ellen McCann. I'm at Boston Children's Hospital as a pediatric

anesthesiologist.

DR. MORRATO: Good morning. I'm Elaine Morrato. I'm an epidemiologist at the Colorado School of Public Health and associate dean for public health practice.

DR. GALINKIN: I'm Jeff Galinkin. I'm a pediatric anesthesiologist at the University of Colorado and a medical safety officer at CPC Clinical Research.

MS. ROBOTTI: I'm Suzanne Robotti. I am the president of MedShadow Foundation and the executive director of DES Action USA.

DR. HIGGINS: I'm Jennifer Higgins. I'm the AADPAC consumer representative.

DR. BATEMAN: Brian Bateman. I'm an anesthesiologist at Brigham and Women's Hospital and associate professor at Harvard Medical School.

DR. PORTER: Laura Porter. I'm a colon cancer survivor and a patient representative, and an independent patient advocate.

DR. MICHNA: I'm Ed Michna. I'm an anesthesiologist pain physician at Brigham and

Women's Hospital in Boston.

DR. KOTZ: I'm Margie Kotz, and I'm a professor of psychiatry and anesthesiology at Case Western Medical School in Cleveland, Ohio and medical director of their addiction recovery services there.

DR. ZACHAROFF: Good morning. I'm Kevin Zacharoff. My expertise is in anesthesiology and pain medicine. I am faculty and clinical instructor in the Department of Preventive Medicine at the State University of New York Stony Brook School of Medicine and the ethics committee chair at St. Catherine of Siena Medical Center in New York.

DR. ARFKEN: Cynthia Arfken. I'm an epidemiologist, professor of psychiatry at Wayne State University.

DR. HABEL: Laurie Habel. I'm an epidemiologist and associate director at the Division of Research at Kaiser Permanente in Northern California.

DR. HUMMEL: Good morning. I'm Michele

Hummel. I'm a pharmacologist. I'm filling in today as an alternate industry rep.

DR. McCANN: Thank you all.

For the topics such as those being discussed today at today's meeting, there are often a wide 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 chairperson. We look forward to a very 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 this 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, the FDA will refrain from discussing the details of this meeting with the

media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks and lunch. Thank you.

Now I will pass it 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 representative, 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 these committees' compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208, is

being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of 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 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of new drug application NDA 209257, proposed trade name Hydexor, a fixed-dose combination oral tablet submitted by Charleston Laboratories, Inc., that contains hydrocodone, acetaminophen, and promethazine, for the short-term management of acute pain severe enough to require an opioid analgesic while preventing and inducing opioid-induced nausea and vomiting. The committees will also discuss the abuse potential of this non-abuse-deterrent product and whether it should be approved. This is a particular matters meeting during which specific matters related to Charleston Laboratories' NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict

of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we'd like to disclose that Dr. Michele Hummel is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Hummel's role at this meeting is to represent industry in general and not any particular company.

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

FDA encourages all other participants to

advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. McCANN: We will not proceed with the FDA's introductory remarks from Dr. Sharon Hertz.

FDA Opening Remarks – Sharon Hertz

DR. HERTZ: Good morning, Dr. McCann, members of the AADPAC and DSaRM, and invited guests. This morning you'll hear about the efficacy and safety data submitted in support of a novel, immediate-release, fixed-dose combination formulation of hydrocodone, acetaminophen, and promethazine, and that's also being referred to with the proposed trade name of Hydexor.

This product was not formulated to have any abuse-deterrent properties, but none of the approved immediate-release, hydrocodone, acetaminophen products have abuse-deterrent properties either. The addition of promethazine to the hydrocodone and acetaminophen combination is intended to reduce or prevent the occurrence of opioid-induced nausea and vomiting, which I think

many people here know can be a major problem for some patients receiving opioids for pain. There are clinical studies conducted in patients who are prone to opioid-related nausea and vomiting.

The applicant was asked to conduct an assessment of the abuse potential of the product Hydexor compared to hydrocodone and acetaminophen. That is because there have been questions about whether or not the addition of promethazine could change the abuse potential either due to additional CNS related effects or by reducing adverse events.

We're also going to provide you information on drug utilization for related products as well as what we can glean from the epidemiologic literature that's relevant for today's meeting. At the end of this morning, we're going to ask you to consider what you've heard and give us advice about the data and what the data support in terms of possible approval and indication.

Thank you very much. We appreciate you taking time from your very busy schedules to be here to help us, and with that, I will let the

meeting get started.

DR. McCANN: 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, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in a sponsor, including equity interest and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any 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 Charleston's presentations.

Applicant Presentation - Thomas Smith

DR. SMITH: Thank you.

Good morning, members of the committee, FDA, and guests. My name is Tom Smith, and I'm the chief medical officer of Charleston Laboratories. Charleston was founded over a decade ago by people who experienced the burden of nausea and vomiting from illnesses like migraine medication such as opioids and everyday events like motion sickness. I'm sure many of us here today have had similar experiences.

Charleston's mission is grounded in the premise of improving acute pain management and preventing nausea and vomiting. We are committed to providing safe and effective therapies to help patients with acute therapies for pain in responsible ways, and as a board certified physician in family medicine for almost 30 years, I understand this burden of nausea and vomiting that our founders sought to address.

I have seen the debilitating effects of nausea and vomiting, but I've also seen the tendency of physicians to prescribe 1 to 2 tablets of an immediate-release opioid every 4 to 6 hours. This has left patients directing their pain management with up to 12 tablets a day and has left a lot of unused medication available for abuse, misuse, and diversion.

So why are we here today? First, because there's a need for better options to manage acute pain while preventing and reducing opioid-induced nausea and vomiting. Second, we're here because we recognize that we are proposing to introduce Hydexor during a national crisis of opioid abuse. We are committed to being a part of this national movement to address this crisis by fostering responsible use of Hydexor and through our initiatives to reduce the number of unused tablets available for abuse, misuse, and diversion. But first we must focus on the gravity of the condition.

As with chemotherapy-induced nausea and

vomiting, or CINV, and postoperative nausea and vomiting, or PONV, we have a responsibility to give voice to patients who are suffering from opioid-induced nausea and vomiting now known as OINV. OINV is common, burdensome, and costly. Approximately 40 percent of patients prescribed an IR opioid report nausea and about 20 percent report vomiting.

OINV places a significant burden on patients in their recovery, on the healthcare system, and on poor patient outcomes, and increased costs. OINV is the primary reason for nonadherence or discontinuation of IR opioids, and once it occurs, OINV is difficult to control, and there are no approved therapies for pain and OINV.

Hydexor is a unique formulation using well characterized analgesic and antiemetic compounds supported by a robust clinical development program. As noted, Hydexor is not intended to be an abuse-deterrent formulation, but we are proposing a comprehensive and innovative abuse-deterrence program.

Hydexor contains immediate-release hydrocodone and acetaminophen as used in Norco and Vicodin, along with a novel formulation of promethazine, the active ingredient in Phenergan. As we began formulation in 2007, the hydrocodone and acetaminophen doses were selected primarily because the combined dosage was commonly prescribed for the immediate care of acute pain, and we were also desiring to limit daily acetaminophen total dose. We selected the lowest oral solid dose of promethazine, which is half of what's typically prescribed today for nausea and vomiting. This is the basis of our engagement with the FDA and the acknowledgment of this novel treatment with a novel indication.

As you'll hear this morning, we have met the requirements for approval under the 505(b)(2) regulatory pathway. This NDA is supported by a comprehensive development program that establishes bioequivalence to the RLDs in Norco, efficacy over Norco for prevention of opioid-induced nausea and vomiting, and a safety profile consistent with the

individual components for the short-term management of acute pain and prevention of opioid-induced nausea and vomiting. And finally, in our human abuse liability study, we saw no increase in abuse potential at supratherapeutic doses.

Our proposed indication is for the short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing OINV, but the treatment itself is only part of the solution. We're also committed to an abuse-deterrence program designed to help reduce the number of unused tablets available for abuse and misuse.

We've heard FDA commissioner Dr. Scott Gottlieb stress the importance of limiting treatment duration, and we agree. Our proposed labeling is generally less than 14 days, and we've proposed a dosing schedule of 1 tablet every 4 to 6 hours as needed for a maximum daily dosage of 6 tablets as compared to what we commonly see today, up to 12 tablets per day and often for more than 14 days.

Rather than expanding the use of IR opioids, Hydexor is intending to displace existing IR opioids for adult patients at risk of OINV. Physicians can best determine those patients at risk of OINV using questions that they're already asking their patients. It should be used with caution in the elderly, and it is not intended for pediatric use or in any patient with medical conditions that would pose a risk.

WE will introduce other approaches to reduce the availability of unused tablets. First, in agreement with the FDA, we will implement an interim REMS for Hydexor until the classwide REMS for IR opioids has been approved. Our interim REMS will include a medication guide, communication plan, and an annual healthcare provider education assessment.

At the core of our REMS is our labeling for short-term use with a maximum of 6 tablets per day, and we have developed a first-in-class 3, 5, and 7-day packaging to better address duration of therapy for IR opioids. We believe that this novel

packaging will encourage necessary and more frequent patient-physician interaction.

Knowing that the legal and operational challenges are vast, we are also developing a first-in-class opioid buyback program known as HydexorReturn that would allow patients to return unused tablets for their proper disposal. In addition, we will conduct the appropriate education, distribution, pharmacovigilance, monitoring, and surveillance programs, and our responsible commercialization efforts will be directed towards select surgeons and acute pain specialists.

Here you can see the remaining agenda. Dr. TJ Gan from Stony Brook University will discuss the medical need, then Dr. Sandy Comer from Columbia University will review our human abuse liability data and share her thoughts on the abuse potential for Hydexor. Next, Dr. Bernard Schachtel, our chief scientific officer, will describe our clinical development program and discuss the efficacy results, then I'll return to

share our clinical safety data and characterize our safety profile, discuss our commitment to risk mitigation and responsible use, and close with a summary of the benefit-risk assessment for Hydexor. We also have some additional experts here today to help address your questions.

Now I'd like to invite Dr. Gan to the podium to discuss the need for new treatment options. Dr. Gan?

Applicant Presentation - Tung Joo Gan

DR. GAN: Good morning. My name is Dr. TJ Gan. I'm a professor and chairman of the Department of Anesthesiology at Stony Brook School of Medicine. I'm a consultant to the sponsor, but I have no financial interest in the outcome of this meeting.

I'm delighted to speak with you about an area that is a particular interest of mine, the management of acute pain and nausea and vomiting. Specifically, I will be discussing the need for immediate-release opioid analgesics that also address a very specific complication associated

with this treatment, nausea and vomiting.

The Federation of State Medical Boards defines acute pain as the normal predictable, physiological response to a noxious chemical, thermal, or mechanical stimulus, and typically it's associated with invasive procedures, trauma, and disease. Acute pain generally is time limited lasting six weeks or less. In cases where other therapies may not be adequate, opioid analgesics can be an essential therapy. Opioids are effective analgesics with a known benefit-risk profile, and the duration of acute pain that requires treatment with an opioid is usually much shorter than the six weeks noted above.

When Scully and colleagues reviewed data on opioid-naive surgical patients, they found the optimal length of opioid prescriptions lies between 4 and 15 days depending on the procedure. When we think about opioids for acute pain, we should be thinking of about 1 to 2 weeks.

Although opioids can be an effective treatment when other therapies are ineffective,

opioid-induced nausea and vomiting is very common and a troubling side effect. Studies show that up to 40 percent of patients report nausea while taking their opioid medication and 20 percent report vomiting, which can lead to inadequate analgesia. Once it occurs, OINV is difficult to control, and there are no approved therapies for acute pain and OINV.

As clinicians, we are able to identify patients at risk. The same risk factors known for postoperative nausea and vomiting apply to opioid-induced nausea and vomiting, and they are age, gender, history of postoperative nausea and vomiting or motion sickness, non-smoking, and the use of postoperative opioids.

Research from Apfel and colleagues found the risk factors for nausea and vomiting have an additive effect. The presence of one risk factor is associated with up to 20 percent incidence of postoperative nausea and vomiting while the presence of 4 risk factors is associated with up to 80 percent incidence. From these data, clinicians

can identify patients at risk.

OINV places significant burdens on patient recovery and clinical outcomes and has definite economic impacts. For the patient, OINV can lead to delays in functional recovery from surgery. It affects their ability to eat, which can impair wound healing, decrease immune function, and increase postoperative complications. Decreased mobility can lead to respiratory and urinary complications, deep vein thrombosis, and constipation, and OINV can cause such discomfort that patients are often willing to sacrifice degrees of pain relief to experience less nausea and vomiting.

As a clinician who is trying to help patients, I am distressed by this unacceptable trade-off, and there are important clinical implications as well. Following surgery, nausea and vomiting can lead to less effective pain management and can increase a patient's time in the hospital by up to 25 percent. Vomiting and wretching are common and are known to cause

surgical complications such as aspiration pneumonia, bleeding, and wound ruptures. There are also significant economic implications. Patients who experience nausea and vomiting have significantly more unexpected hospitalizations, hospital and doctor visits, and emergency room visits.

What is the mechanism of OINV? Opioids activate the mu copper and delta receptors in the CNS, triggering emetic pathways in the chemoreceptor trigger zone, or CTZ, leading to the vomiting center, which initiates the nausea and vomiting episode. Hydexor seeks to prevent and reduce OINV with the addition of promethazine.

But why is promethazine a good choice? Promethazine addresses the pathophysiology of OINV. It inhibits the three receptors involved in OINV, which can prevent and reduce nausea and vomiting. Promethazine has a long history of safe and effective use and has not been associated with side effects such as QT prolongation, which are common with dopamine antagonists and seratonin

antagonists.

The promethazine dosing recommendation of 12.5 milligrams every 4 to 6 hours allows for safe multidosing on the same schedule as immediate-release opioids, and a maximum daily dose of promethazine in Hydexor is half the maximum approved daily dose of 150 milligrams of commercial promethazine.

In summary, the short-term use of immediate-release opioids is necessary for some acute pain patients, but the associated nausea and vomiting presents significant burdens to patients and the healthcare system, and there are no approved therapies for acute pain and OINV.

Hydexor represents a novel approach to address these challenges. The low dose of promethazine contained in Hydexor blocks the underlying mechanisms of OINV. Patients with acute pain would benefit from access to a single proven therapy that not only relieves their pain but also prevents OINV. Thank you.

Now I would like to invite Dr. Sandra Comer,

professor of clinical and neurobiology, College of Physicians and Surgeons, Columbia University, to discuss Charleston's human abuse liability study and provide a perspective on the potential for abuse of Hydexor. Dr. Comer?

Application Presentation - Sandra Comer

DR. COMER: Good morning. I'm Sandy Comer. I'm a clinical research scientist focused on testing novel compounds for the treatment of opioid dependence and studying the relationship between pain and opioid abuse. I'm a consultant to the sponsor but I have no financial interest in the outcome of this meeting.

I'd like to discuss what is known from the literature about the abuse potential of hydrocodone and promethazine and how current prescribing patterns contribute to the availability of excess tablets for abuse and misuse, then I'd like to review Charleston's human abuse liability study and discuss what other information we can take from their clinical program to address abuse potential.

Both the FDA and Charleston reviewed

epidemiological data on the abuse of hydrocodone and promethazine. As you saw in the FDA's briefing document, the number of prescriptions written for hydrocodone APAP has declined in recent years, but hydrocodone APAP is still the most widely prescribed opioid.

When Cassidy and colleagues reviewed substance abuse data from the NAVIPPRO surveillance system, they found that hydrocodone APAP is still the most frequently reported opioid abused, but when they adjusted for the number of prescriptions dispensed, hydrocodone APAP's abuse rate was the lowest among the opioids examined. So it would appear the availability of hydrocodone APAP is a factor in its abuse.

We also see from the NAVIPPRO data that the vast majority of hydrocodone APAP abuse occurs orally. This finding is further supported by research from Katz and colleagues. When we consider ways to deter hydrocodone abuse, we need to focus on this route of administration.

We also know that length of opioid exposure

is a predictor of abuse. Brat and colleagues found that misuse increased by 44 percent for each refill and 20 percent for each additional week of opioid use. As shown here in green, prescriptions of less than 2 weeks were associated with the lowest rates of abuse, so reducing the length of opioid prescriptions may have a positive effect on abuse.

As I mentioned earlier, there's been a decline in the number of prescriptions written for hydrocodone APAP. Here we see data from IQVIA National Prescription Audit on the annual number of opioid prescriptions in green and total hydrocodone APAP prescriptions in blue.

As you can see, the number of prescriptions is declining, however, the number of pills dispensed per prescription has actually increased as shown here by the dashed line. This may be related to the rescheduling of hydrocodone from Schedule III to Schedule II. Since physicians can no longer call in a refill for Schedule II products, there may be a tendency to write larger initial prescriptions. And this is important

because the availability of unused tablets is a factor in abuse.

When Bicket and colleagues reviewed six studies involving surgical patients, they found that 67 to 92 percent of patients had unused opioids available after completing treatment. In fact, up to 71 percent of dispensed pills went unused.

So what happens to those unused tablets? Data from SAMHSA's National Survey on Drug Use and Health shows that unused pills become a supply for abuse. Most survey participants obtained opioids for non-medical use from family and friends, or dealers, rather than from their own prescriptions. This further demonstrates the need to reduce the number of tablets available.

Turning now to promethazine, the prevalence of promethazine abuse is unknown, but it does occur often in combination with an opioid. There have been reports of cough syrup containing codeine and promethazine being abused since the 1990s, and Clatts and colleagues found that in the mid 2000's,

heroin users in southeast Asia commonly abused intravenous promethazine either to substitute for inadequate heroin supplies or to reduce opioid withdrawal symptoms.

In addition, an NIH-sponsored study by Lynch and colleagues found that approximately 9 percent of chronic pain patients tested positive for promethazine, while only half of those had an active prescription for it. This was more common among patients using extended-release opioids. Literature and surveillance symptoms note some associated morbidity and mortality, but the reasons stated for promethazine abuse are varied, and it's not clear whether opioid-promethazine combinations are more desirable than opioids without promethazine.

Following both the FDA and Charleston's reviews of the epidemiology, we see that hydrocodone and promethazine are commonly used in ways not directed by a healthcare provider, which contributes to morbidity and mortality. We also see that hydrocodone is primarily abused orally, so

when we consider abuse deterrence, there should be a focus on steps that address oral abuse. And we know that the number of excess pills contribute to the supply of pills for abuse, so reducing the duration of use and the availability of excess tablets may help reduce opportunities for abuse and diversion.

We also know that misuse and abuse of promethazine and opioids occur together in some areas and among some demographic groups. Anecdotal evidence suggests varying reasons for this, but while we know the abuse occurs, the available epidemiologic data are not informative as to whether Hydexor is more likely to be abused or whether the addition of promethazine adds to the risk profile.

To help answer these questions, Charleston conducted a dedicated human abuse liability study. It was a 5-arm crossover study that compared Hydexor versus placebo versus hydrocodone and acetaminophen without promethazine. Comparisons were made at supratherapeutic doses 3 and 5 times

the recommended dose. The primary endpoint was the maximum effect of drug liking on a bipolar visual analog scale from 0 to 100, where a score of 50 was neither like nor dislike the effect at the moment.

The sample size was intended to provide greater than 95 percent confidence to detect a significant difference between the active and placebo groups. For my own research, the human abuse liability studies I conduct often have much smaller sample sizes, but they still have high predictive value, so the sample size used in study 007 was more than adequate.

Sixty-one subjects were randomized to the qualification phase and were given a naloxone challenge to ensure that they were not physically dependent on opioids. Later, they received 30 milligrams of hydrocodone with 1300 milligrams of acetaminophen to determine whether they could tolerate the treatment and distinguish it from placebo.

Subjects with greater than or equal to a 15-point difference between placebo and HC-APAP on

drug liking response were randomized to the treatment phase. Forty subjects received each of the 5 treatments in a random sequence. All study medications were over encapsulated in identical capsules for double-blinding. Assessments were made over 24 hours with a minimum washout period of approximately 72 hours between each treatment.

The results show that the addition of promethazine did not increase drug liking, which was the primary endpoint of the study. On this scale, a score of 100 represents a strong liking, 50 represents neither like nor dislike, and zero is a strong disliking.

At both supratherapeutic doses 3 and 5 times the therapeutic dose, there were no statistically significant differences between Hydexor and hydrocodone APAP. This observation of no significant difference was seen consistently across the majority of the secondary measures, including high, in which subjects were asked to rate their feeling on a scale from not high at all to extremely high and take drug again, where subjects

were asked about their desire to use this drug in the future.

Charleston also evaluated potential abuse, misuse, and diversion by analyzing the drug accountability data across their clinical trial program. In studies 002 and 003 when patients were sent home with Hydexor, nearly all unused tablets were returned. In study 006 where patients were given a 14-day supply of Hydexor, nearly 99 percent of unused tablets were returned.

As compared to similar controlled opioid studies, these accountability numbers are quite good, and they're reassuring in that they do not suggest a tendency toward increased misuse or diversion in the clinical studies.

Based on the clinical data, the addition of promethazine does not appear to increase Hydexor's abuse potential. I'm reassured by these results. In my experience, these studies are good predictors of what happens in actual use. Study 007 also demonstrated that at 3 and 5 times the therapeutic dose, Hydexor was associated with greater sedation

compared to HC APAP, but this did not have a significant effect on drug liking.

As a safety topic, it is addressed in the proposed warnings and precautions, and like all opioids, regardless of abuse-deterrent formulation, Hydexor will carry a black box warning regarding its potential for abuse, misuse, and diversion. And maybe most importantly, I was really impressed when I read the briefing document from Charleston Labs about their plans to reduce and misuse; their limiting the number of tablets that they're dispensing or giving out to patients; their instituting a buyback program, which is really novel and something I haven't seen before and I think is a great idea; and their limiting the dose of product that's in each tablet.

I think all of these kinds of ideas and plans that they have in place will really be important in trying to reduce the abuse of this type of product. Thank you. And now I'd like to invite Dr. Bernie Schachtel to discuss the clinical development program for Hydexor.

Applicant Presentation - Bernard Schachtel

DR. SCHACHTEL: Bernie Schachtel. Good morning, everyone. I'm the chief scientific officer at Charleston Laboratories. Thank you for the opportunity to present the data from our clinical development program that supports the efficacy and safety of Hydexor as a treatment for acute pain while preventing and reducing OINV.

We evaluated the safety and efficacy of Hydexor in a comprehensive clinical program. We evaluated relative bioavailability in three pharmacokinetic studies. We conducted two large randomized pivotal studies to evaluate efficacy and safety in two different acute models. We conducted an actual-use safety and effectiveness study in patients with acute flares of osteoarthritis. And as you've just heard, we also conducted a human abuse liability study. Overall, these studies enrolled more than 1300 subjects.

Our bioequivalence studies use a standard crossover design. Study 004, which is shown here, demonstrated bioequivalence of Hydexor to the

reference-listed drugs in both fasted and fed conditions. Studies 012 and 013 established the bioequivalence of the hydrocodone in Hydexor to the hydrocodone in Norco, which was the active control in the clinical studies. Together these data established the pharmacokinetic bridge required under the 505(b)(2) pathway.

Next, we'll examine the efficacy results from the two pivotal trials, 002 and 003. These two phase 3 trials were conducted in standard acute pain models, oral surgery and bunionectomy. As described in your briefing document, both studies had entry criteria that were intended to enrich the study with patients who may develop OINV. This study design feature was included to help delineate more clearly and more efficiently a difference in the incidence of OINV between patients who are treated with Norco and patients who are treated with Hydexor in the studies.

Patients with moderate or severe pain after surgery were randomized to receive Hydexor, Norco, or placebo under double-blind conditions. In

study 002, dosing was every 4 to 6 hours as needed over 5 days. In study 003, patients were dosed 5 times per day for the first 48 hours, then every 4 to 6 hours as needed over the remaining 3 days. Patients recorded hourly the intensity of nausea, the intensity of pain, and the frequency of vomiting through 24 hours in the 002 study and through 48 hours in the 003 study, which were the primary evaluation periods for each study.

There were two co-primary endpoints, pain reduction by Hydexor compared to placebo and the reduction in the incidence of OINV comparing treatment with Hydexor to the positive control Norco. Additionally, as discussed with the agency, we prospectively and actively measured other opioid related adverse events on opioid symptom scales.

Both studies met their co-primary endpoints. In study 002, some pain intensity differences over 24 hours demonstrated that Hydexor provided significant pain reduction compared with placebo. In study 003, the SPID-48 analysis demonstrated significant pain reduction compared with placebo

over 48 hours.

The co-primary OINV endpoint was also met in study 002. The incidence of OINV was 22 percent in absolute terms, 22 percent lower in the Hydexor treatment group than the Norco group, a difference that represents 38 percent relative reduction in the risk of developing OINV.

In study 002, OINV was defined as a composite endpoint with three components: any moderate or severe nausea; any use of a rescue antiemetic; and any occurrence of vomiting. Based on feedback from the FDA, we also assessed their preferred definition of OINV, which has two criteria: any use of a rescue antiemetic, which FDA regards as a surrogate for significant nausea; or any occurrence of vomiting. Using this two-component definition of OINV, the relative risk reduction was 64 percent in study 002. This definition was used as a co-primary OINV endpoint in study 003, and here we observed a 74 percent relative reduction in the risk of developing OINV.

We also observed consistent evidence of the

efficacy of Hydexor across the prespecified key secondary endpoints in both trials. In study 002, for example, compared to treatment with Norco, we see the effect of Hydexor on the intensity of nausea over the treatment period, and on the right is the effect of Hydexor compared to Norco on the frequency of vomiting.

Here from study 003, we see the effect of Hydexor compared to Norco on the development of post-discharge nausea and vomiting. In the middle, you see the effect of Hydexor and the need for rescue antiemetics and the frequency of vomiting. A description of these prespecified secondary endpoints in these studies is found in your briefing document. Among them is a comparison of the rates of complete response among patients treated with Hydexor compared to Norco.

Shown here over the 5-day treatment periods of studies 002 and 003 are the results using the FDA definition of complete response, which is "no emetic episode and no use of rescue antiemetic." In both studies, there was significant evidence of

the durability of the prevention of OINV with Hydexor treatment.

To conclude, Hydexor was shown to be bioequivalent to Hydexor, acetaminophen, and promethazine, and the pivotal phase 3 trials demonstrated that Hydexor significantly reduced pain and the risk of developing opioid-induced nausea and vomiting. Based on these results, we conclude that Hydexor can be an effective medicine for the short-term treatment of acute pain and for the prevention and reduction of OINV, improving pain management and patient recovery.

Thank you, and now I'll turn it over to Dr. Smith to discuss the safety results for Hydexor.

Applicant Presentation - Thomas Smith

DR. SMITH: Thank you, Dr. Schachtel.

Now that we've seen the efficacy data from our clinical program, I'll address our safety data. We realize that the ingredients in Hydexor are widely used and well known. That said, we're well aware of the potential risk, and we took a

proactive approach in understanding its safety profile.

In this extensive evaluation, we found no new specific safety concerns. Adverse events were mostly mild to moderate in severity and limited in duration. The most commonly found event, whether proactively solicited or spontaneously reported, was drowsiness. As expected with the addition of promethazine, drowsiness was more common with Hydexor than with Norco. Consistent with the alpha-adrenergic blocking effects of promethazine, there was also an increased incidence of lower blood pressures observed within the first 24 hours. We saw no respiratory depression.

All of these adverse events resolved and all subjects completed the studies without dose interruption or drug discontinuation and without any consequences of sequelae. The proposed label indication is for short-term use, and all known adverse events that are addressed in the warnings and precautions of the reference-listed products are also included in the proposed label for

Hydexor.

I'll start with a discussion of the safety results from our two pivotal studies 002 and 003 and then review additional safety data from the open-label, actual-use safety study 006. We conducted a pooled analysis of safety for the two randomized pivotal studies. It's important to remember that in these studies, opioid symptoms were solicited by a directive questionnaire, and nausea and vomiting were efficacy endpoints. All other adverse events were captured in a conventional, spontaneous, and non-directive fashion.

Due to differences in collection methods, I will present adverse events actively solicited separate from other adverse events. Of note, across the three phase 3 studies that enrolled nearly 1200 patients, there were a total of 3 SAEs, none of which were considered related to study medication.

We used the OSS questionnaire for active AE collection. The OSS was adapted from the opioid

related Symptoms Distress Scale, or SDS, which was developed to measure common adverse events in the postoperative setting. With the exception of nausea and vomiting, which were clinical endpoints, we adjusted the SDS to assess these 9 additional side effects shown here. Each symptom was rated on a Likert scale ranging from zero or none to 10 or severe. The OSS was administered at baseline and periodically following drug administration.

In order to fully understand Hydexor, we thought it necessary to actively solicit each of these important opioid related symptoms. For context, to be included in this bar chart, a subject needed to acknowledge an event on just a single occasion. As you can see, most opioid related symptoms occurred at similar rates in the Hydexor and Norco groups in the pooled studies.

Drowsiness was the most commonly reported of these symptoms across all three treatment groups, occurring in 93 percent of patients in the Hydexor group, 89 percent in the Norco group, and 69 percent in the placebo group. As would be

expected following a surgical procedure, many patients reported drowsiness pretreatment.

Consistent with the inclusion of promethazine and Hydexor, slightly higher numbers were observed with Hydexor versus Norco for certain CNS events. The majority of these were assessed as mild to moderate in intensity and again were without sequelae or consequence. In both pivotal studies, the mean severity of most side effects over the 5-day treatment period in both active treatment groups was mild. The exception was drowsiness in the Hydexor group where the mean severity was in the moderate range.

Let's look now at the severity of spontaneously reported adverse events, the conventional categories used in clinical trials. Across all three treatment groups, more than 90 percent of the adverse events were categorized as either mild or moderate in severity by the investigators, and the rates of mild and moderate events were comparable between the Hydexor and Norco groups.

No patient in the Hydexor group had his or her dose reduced or interrupted or withdrew from the study due to an adverse event. As noted in the briefing document, there were three serious AEs across the entire program, 2 in the Hydexor groups and 1 in a Norco group. None were considered related to study drug.

Given the known safety profiles of the active ingredients in Hydexor, these are the events of special interest. As you can see, with the exception of promethazine and syncope, the incidence of these events was low or absent and similar between Hydexor, Norco, and placebo. Hypotension was reported as an AE in 3 patients in each of the active treatment groups, but no patients had a reduction in dose or discontinued due to hypotension.

When we looked more broadly at systolic and diastolic blood pressures across these studies, we observed an increased incidence of lower blood pressures among the Hydexor patients within the first 24 hours. This observation is consistent

with the alpha-adrenergic blocking effects of promethazine and will be addressed in our proposed label. In addition, there was no respiratory depression observed.

When we examined the AESIs in greater detail, we found that none were deemed severe by the investigators, none resulted in dose reduction, study drug interruption, or discontinuation. None resulted in clinically significant consequences or sequelae, and all resolved without reoccurrence while on treatment. As with the labels of the reference-listed drugs, these events are noted in the proposed label for Hydexor under warnings and precautions.

Turning now to study 006, recall that it was designed to provide additional exposure data in an actual-use setting. Study 006 enrolled osteoarthritis patients whose pain from acute flares was not adequately controlled with non-steroidals and were opioid naive. Patients were taken off of NSAIDs and other arthritis treatments.

Patients who reported acute flares of OA

were evaluated for inclusion. Those included were directed to take Hydexor every 4 to 6 hours as needed for pain. This patient population was not enriched for OINV and adverse events were collected through spontaneous reporting via patient diaries. 179 patients were enrolled and all but one received study drug. Ninety-seven percent of enrolled patients completed this study.

This study provided additional data in older patients as well. The mean age was 61.2 years and 37 percent of the patients were older than age 65. The typical patient was white, female, and with a body mass index of 29. At baseline, 46 percent had moderate pain and 53 percent had severe pain.

A total of 185 adverse events were reported by 81 patients in study 006. The majority of events were of mild or moderate severity, and the most frequent events were drowsiness and dizziness. Again, these are expected side effects of both hydrocodone and promethazine, so the Hydexor proposed label is consistent with the labels of the reference-listed drugs and includes the same

warnings and precautions. Only 4 patients reported nausea and vomiting, and as noted in the briefing document, patients reported improvements in joint pain, in stiffness, and activities of daily living.

To summarize our safety results, each of the ingredients in Hydexor is widely used and well known, producing a manageable and predictable safety profile. No new specific safety concerns were identified during the phase 3 pivotal studies, or the actual-use safety study, or in any of the dedicated clinical pharmacology studies.

Overall, the clinical program demonstrated that Hydexor was generally well tolerated with side effects that were mostly mild or moderate in intensity and limited in duration. The most commonly reported adverse event was drowsiness, which was more frequent with Hydexor than with Norco.

We also observed an increased incidence of lowered blood pressures among the Hydexor patients within the first 24 hours, which is consistent with the conclusion of promethazine. All known adverse

events that are addressed in the warnings and precautions of the reference-listed products are also included in the proposed label for Hydexor.

Turning now to our plans for responsible stewardship of Hydexor, we recognize that the public health crisis of opioid abuse, which is occurring. Federal and state authorities across the nation are confronting this crisis, and we want to be a part of this movement. We are committed to fostering responsible prescribing and safe use of Hydexor, and we are proposing innovative steps to help limit duration, control dosing, and reduce the number of unused pills available for abuse, misuse, and diversion.

First, in agreement with the FDA, we will implement an interim REMS for Hydexor until the classwide REMS for IR opioids has been improved. Our interim REMS will include the package insert for healthcare provider education, a medication guide for patients, a communication plan for educating all stakeholders, and an annual healthcare provider education assessment.

At the foundation of our REMS is our proposed label. We agree with the FDA that the medical community should limit the quantity of opioid analgesics being prescribed and dispensed. To achieve this objective, we have taken two important steps.

First, we've defined short-term use for acute pain as generally less than 14 days, which was stated both in our proposed label and our medication guide for patients. Second, we have a proposed dosing schedule of 1 tablet every 4 to 6 hours as needed for a maximum daily dosage of 6 tablets. This is a departure from the current practice of prescribing IR hydrocodone, which is 1 to 2 tablets every 4 to 6 hours for a total of up to 12 tablets per day.

To further moderate dosing and reduce the potential availability of unused product, we are proposing 3, 5, and 7-day packages. They will be F1 child-resistant packs with a total of 18, 30, or 42 tablets, respectively. This packaging is designed to meet the expectations of the FDA and

state representatives to reduce the size of opioid prescriptions for acute pain.

We realize that we may alienate some clinicians with these quantity limits, however, we strongly feel as an organization that this change is long overdue. It aligns with the research Dr. Gan just cited regarding the optimal duration of therapy in this setting and the data that Dr. Comer noted regarding quantity of unused tablets under current prescribing practices.

We are also taking a responsible commercialization approach. Our logistics partners have extensive experience with Schedule II opioid analgesics and will work in coordination with us to report any suspicious ordering, dispensing, and distribution activities. We are working with them and others to develop a first-in-class opioid buyback program known as HydexorReturn that would allow patients to return unused tablets for their proper disposal. Together we are working to resolve the potential legal, regulatory, and operational challenges to launch such a plan.

In addition, all customer-facing personnel will be trained on best practices in acute pain, addiction medicine, OINV, and the appropriate use of Hydexor. Our ongoing monitoring will track patient experience in use, physician prescribing patterns, and trends in pharmacy ordering and dispensing. Our pharmacovigilance program will provide ongoing safety monitoring and reporting to the FDA and other stakeholders.

Finally, to help with our annual REMS effectiveness assessments, provide guidance on our HydexorReturn buyback program, and consult on other risk mitigation efforts, we are forming an independent risk mitigation advisory board. Our risk mitigation advisory board will include experts in abuse and addiction, drug enforcement, acute pain management, and related fields.

To summarize our approach, we will foster responsible use of Hydexor through REMS and our abuse mitigation program. In addition, our labeling and packaging and the buyback program that we are exploring are all intended to help reduce

the number of unused tablets available for abuse, misuse, and diversion, and we will employ comprehensive programs for education, distribution, pharmacovigilance, monitoring, and surveillance. Finally, our launch focus will be limited to select surgeons and acute pain specialists.

To conclude our presentation, I'd like to provide our assessment of the benefit-risk profile for Hydexor. First, it's important to remember that we are addressing an unmet need. As Dr. Gan discussed, OINV is a common occurrence that places significant burdens on patient recovery, clinical outcomes, and the healthcare system.

The benefits of Hydexor are clear. Hydexor significantly reduced pain and prevented OINV. These results were consistent across secondary endpoints and were durable. The safety profiles of hydrocodone APAP and promethazine are well characterized, and when combined in Hydexor, we see no new safety signals. There is an increased risk of drowsiness, and this is noted in our proposed label.

We recognize that we are proposing to introduce Hydexor during this national crisis of opioid abuse, and all of us are charged with considering the public health implications of the potential for abuse of Hydexor. But as we heard from Dr. Comer this morning, while we did not see evidence of increased abuse in the human abuse liability study, we're taking comprehensive and innovative approaches to mitigate the risk of abuse, misuse, and diversion. Taken together, our clinical data and our commitments show that the benefits of Hydexor outweigh the risk.

Thank you. We look forward to your questions and discussions later this morning.

DR. McCANN: Before we start with clarifying questions, could we have Dr. Ciccarone introduce himself?

DR. CICCARONE: Good morning, everyone. My apologies for being late. Dan Ciccarone, professor of family and community medicine, UCSF.

Clarifying Questions

DR. McCANN: Thank you.

If we could have some clarifying questions for Charleston. You can turn your name tag to the side, and then we'll get your name. Dr. Michna?

DR. MICHNA: I have a few questions. As an old pharmacist, I always had trouble with combination drugs. Instead of helping in terms of flexibility, I think they kind of limit it. My question is you have one strength, and you picked 7.5 milligrams. That's higher than the usual dose. So I would think somebody with nausea and vomiting -- why would you give them a supratherapeutic dose? I would think that would increase the chance of nausea and vomiting. So why did you pick 7.5 milligrams?

DR. SMITH: We picked the 7 and a half milligrams of hydrocodone with that acetaminophen because it was a commonly used dose, and we wanted to ensure pain relief in these patients with acute pain on a schedule of up to 6 tablets a day.

That's why we picked it. But along with it, we chose the lowest oral solid dose of promethazine, again, wanting to give patients the

benefit of the relief of the opioid from the nausea and vomiting. So we limited the quantity of promethazine with that.

DR. MICHNA: But the acute pain is self-limiting, and it goes down, so maybe a patient's not going to need 7.5 milligrams. Have you tested half tablet and see if that was equally effective?

DR. SMITH: We have not tested half tablet. No, sir.

DR. MICHNA: Again, pain goes down. There has to be some flexibility here. Maybe patients don't want to take that full dose.

The other thing is do you think that higher dose skewed your data? You're giving higher than normal doses of opioid, so therefore, I would predict that there has to be a dose related phenomenon that more opioid would produce more nausea and vomiting. Do you think that in any way skewed the incidence of nausea and vomiting?

DR. SMITH: I'm going to ask Dr. Gan to address that and to give some more color around

that; if you would, please, Dr. Gan?

DR. GAN: I think the question is about balancing between pain relief and relieving one of the side effects of opioid, which is nausea and vomiting. Certainly, I take your point that everyone's pain may be different, but what I'll argue is that this is the most commonly used dosage. And if a patient has taken, as I typically do, as a PRN basis, that if they do not need to use as much, they don't have to take on this schedule basis.

The other thing I would say is that the promethazine, as we all know, is commonly used in the postoperative setting. And to try to minimize the side effects of promethazine, this dose of promethazine is half what we normally use, which would be typically the prescription if you give a separate opioid as well as promethazine.

DR. MICHNA: Well, I don't know what the data is that 7.5 is a usual dose, since 5 milligrams is the usual dose, and it's 1 to 2 tablets. So I don't know where you -- you may be

averaging whether they take 1 or 2, but I didn't see any of that data that you presented.

The other thing is if you're going to give something orally, why not pre-dose them an hour or an hour and a half in advance? I could give 12.5 milligrams of promethazine, but clinically I would give that an hour and a half before I exposed them to opioids.

DR. HERTZ: This is Sharon Hertz. Very good questions, but this time is just to clarify what the company has presented and further discussion should occur once we're through the open public hearing.

DR. MICHNA: Sure. Okay.

DR. McCANN: Dr. Morrato?

DR. MORRATO: I will try and make mine just clarifying. I had one clarifying around the abuse potential study. Can you describe what was the patient population that was in it, and if they had history of nausea or not the way you define eligibility criteria in the trials?

DR. SMITH: I'll ask Dr. Comer to speak to

that.

DR. COMER: Hi. This is Sandy Comer. The population were recreational opioid users, so they had to have used opioids for recreational purposes at least 10 times in the past year. We didn't show the data, but they were not selected for their propensity to experience nausea and vomiting, but they did experience it during the trial.

DR. MORRATO: But not enough that they weren't using it recreationally.

DR. COMER: Correct.

DR. MORRATO: The second question, I agree that the buyback program is novel, and I'd like to hear more details on its feasibility of implementation and specifics. Have you had discussions with DEA? As a controlled substance, how does someone actually return it? Who benefits from the payment? It might be the insurer or me out of pocket. And to what degree, since these are state regulated, have you actually reached out to individual states?

So I'm really concerned around the

feasibility. It sounds great, but is it really going to happen?

DR. SMITH: Right. Where we're at to date, we are quite committed to this program. We have reached out to a third party, a reputable third party that has experience in supply chain and retail pharmacy. We realize that there are limitations under the Controlled Substances Act and provisions there. But again, as you can imagine, this is quite a process, but we are having conversation currently. We are not yet having conversation with DEA. We have met with some former DEA people to kind of get their input as well to see how this can happen.

I think a good way to look at this is as a reverse distribution model. Just like we get drug out, why shouldn't we be able to get it out of the system as well and back for incineration. We haven't really worked through all the remuneration yet, thinking that perhaps this is a program that the patient, when he or she picks up their prescription, they either sign, opt in or opt out.

We would send them the materials necessary. They would get part of their co-pay back, and then another portion back at the end when everything is accounted for and returned for incineration.

We understand it's a novel program. We're committed to it. I think it's like anything else that's complex. There sounds to be enthusiasm around it from the stakeholders that we've reached out to. It's just how do we implement that, how do we phase it in, to make sure that it happens. But certainly, I think it's a real step in the right direction.

DR. McCANN: We have time for just one last question. We'll take clarifying questions after the FDA presentation, but we'll listen to Dr. Galinkin.

DR. GALINKIN: I actually have two questions, but the first question is quick. Did the patients in the operating room study get Zofran or scopolamine or anything since they're identified as high-risk patients?

The second question is did you do any

multidose PK studies to the maximum time of 14 days, specifically in patients who are cytochrome P450 2D6 metabolizers since promethazine is a CYP2D6 substrate?

DR. SMITH: Right. Again, I'll ask Dr. Gan to address the specifics around what they were dosed with. They could have rescue antiemetics. Actually, maybe Dr. Schachtel, if you would come up and talk about the use of rescue and address that.

DR. GALINKIN: I meant specifically prophylactic in the operating room, more of a standard of care.

DR. SMITH: No, I understood.

DR. SCHACHTEL: Bernie Schachtel. Exactly. No. The answer is no one, no, to your prophylactic -- well understood, since they would obviously contaminate our evaluation, of any prophylactic effects.

Your second question was what?

DR. GALINKIN: The second question is did you do multidose PK studies for promethazine, specifically in CYP2D6 poor metabolizers?

DR. SCHACHTEL: No, I understand. We have considered it. It was deemed unnecessary actually, so we did not conduct that trial.

DR. McCANN: We will now proceed with the FDA presentations.

FDA Presentation - Timothy Jiang

DR. JIANG: I'm Dr. Timothy Jiang with the Division of Anesthesia, Analgesia, and Addiction Products. The sponsor has provided a comprehensive summary of data intended to support the safety and efficacy of Hydexor, and I will provide additional clinical considerations in the agency's evaluation of this application.

My presentation will focus on certain aspects of the study population and safety evaluation as they pertain to the indication under consideration. As you just heard, Hydexor is a fixed-dose combination product containing the analgesic hydrocodone and acetaminophen as well as antiemetic promethazine. Promethazine was included in the combination to mitigate the effects of nausea and vomiting associated with opioid therapy.

The sponsor has proposed the following indication, which incorporates the prevention and reduction of opioid-induced nausea and vomiting in a broad, unrestricted patient population. The proposed indication is novel in which FDA has not previously approved combination products that incorporate both an analgesic component along with a nausea and vomiting component to the indication. Similar to all other currently available analgesic products containing hydrocodone and acetaminophen in combination, Hydexor has not been formulated with features intended to defer abuse.

As you just heard, the sponsor conducted two phase 3 studies to support Hydexor for the proposed indication. Study 002 is a dental pain study and study 003 is a post-bunionectomy pain study. Both studies only enrolled patients that were anticipated to be prone to nausea and vomiting as determined by the results of a nausea-prone questionnaire, NPQ, with or without a hydrocodone challenge.

Based on this assessment, patients were

classified as likely nausea prone or possibly nausea prone. Likely nausea prone was defined a patients having reported nausea or vomiting following previous opioid exposure and/or experienced nausea or vomiting following the hydrocodone challenge. The possible nausea prone was defined as patients having reported nausea or vomiting in the context of a variety of other situations. Additionally, the protocol allowed the investigator to enroll up to 10 percent of patients who did not meet the predefined nausea-prone criteria but were thought to be nausea prone based on clinical judgment.

This table summarizes the results of nausea-prone assessment for the randomized patients in the two phase 3 studies. For both studies, the majority, i.e., 79 percent or 69 percent, of patients were classified as likely nausea prone.

As you just heard, the sponsor proactively evaluated patients for 9 opioid related adverse events, AEs, using the Opioid Symptom Scale, OSS, in the phase 3 studies. Patient rated the severity

of each symptom on a 0 to 10 Likert scale. You have seen the slide in a slightly different version by the sponsor.

This table summarizes the overall results on the opioid symptom scale in the pooled phase 3 studies regardless of the severity. Risk of CNS SAEs such as confusion, difficulty concentrating, and drowsiness were higher in the Hydexor group compared to the Norco group, although it should be noted that placebo treated patients also experienced a fairly high frequency of these AEs, potentially owing to the proactive nature in which these AEs were collected.

However, when you look at the severe AEs on the opioid symptom scale, there is a much cleaner separation between treatment groups with Hydexor treated patients having higher frequency of CNS rated AEs. For example, in the dental pain study, severe drowsiness was experienced by 46 percent of Hydexor treated patients compared to 37 for the Norco. Similar trends were also seen in the post-bunionectomy pain study with severe drowsiness

affecting 42 percent of subjects in the Hydexor group compared to 21 in the Norco group in the first 2 days.

Although the results on the opioid symptom scale demonstrated a relatively modest increase in the CNS AEs for Hydexor compared to Norco, there was a more pronounced increase in the frequency of severe CNS AEs for Hydexor. There were no discontinuations due to AE in the phase 3 program, however, in the open-label safety study 006, there was one subject discontinued from Hydexor due to several AEs, including somnolence. There were no deaths or nonfatal CNS serious AEs that were attributed to Hydexor.

We heard from sponsor that there was a decreased amount of opioid-induced nausea and vomiting, OINV, with Hydexor as compared to Norco as demonstrated on the agency's preferred nausea and vomiting endpoints. The sponsor is proposing a prevention and reduction of OINV indication in a broad, unrestricted patient population requiring opioid and analgesic therapy. However, if Hydexor

was approved, the indication would need to be modified in two important ways: first, to reflect the agency's preferred nausea and vomiting endpoints; and secondly, to reflect a more narrow population based on the observed and potential safety concerns.

The preferred OINV endpoints consist of vomiting or use of antiemetic medication and reflects the prevention of OINV rather than a reduction in the symptoms in patients experiencing OINV, therefore, the appropriate indication for the OINV component would be the prevention of OINV. Also, the indication should be limited to the patients who expect to be prone to opioid-induced nausea and vomiting because this study population was enriched to this type of patient, and a higher frequency of CNS related AEs was observed in the Hydexor group compared to the Norco group, as I just discussed.

Additionally, promethazine is associated with a number of AEs as described in the approving label. Although serious AEs related to

promethazine were not observed in the clinical studies and because not all patients who are treated with opioids experience OINV, it is not appropriate to prescribe a medication to patients who are not expected to realize a benefit. Therefore in closing, the indication must reflect that Hydexor be used in patients who expect to be prone to nausea and vomiting. Thank you.

FDA Presentation - Jennie Wong

LCDR WONG: Hi. Good morning, everyone. My name is Jennie Wong, and I'm a drug utilization analyst in the Division of Epidemiology II in the Office of Surveillance and Epidemiology. I will be presenting analysis on recent drug use patterns of hydrocodone-acetaminophen, and promethazine in the outpatient retail market to provide context for today's discussion.

Here is an outline of my presentation. Using several databases, we focused on analysis of the outpatient retail setting, which was the primary setting of care where the products of interest, namely hydrocodone-acetaminophen, and

promethazine, are used based on sales distribution data. The list here provides the products which were included in our analyses. We focused on hydrocodone APAP products and promethazine-containing products, and also included other selected opioid analgesic products to provide additional context.

This graph shows the nationally estimated number of patients who received a prescription dispensed from retail pharmacies. In this graph, the number of patients who received a dispensed prescriptions for hydrocodone APAP decreased from approximately 45 million patients in 2012 to 37 million patients in 2016. Of note, in October of 2014, the DEA rescheduled hydrocodone combination products from Schedule III to a more restrictive Schedule II. The decline seen may be the result of this action, but we did not assess the factors impacting this decline.

This figure shows the estimated number of dispensed prescriptions for hydrocodone APAP and selected opioid analgesic comparators. Similar to

the patient data, prescriptions dispensed for hydrocodone APAP decreased 34 percent from approximately 125 million to 83 million prescriptions in 2016. For the selected opioid comparators, the prescription volume for combination oxycodone-acetaminophen, hydromorphone and tapentadol declined while prescriptions dispensed for oxycodone, morphine, and oxymorphone increased. Hydrocodone-acetaminophen continued to account for the largest proportion of the selected drugs throughout this time period.

This figure shows the estimated number of prescriptions dispensed for promethazine-containing products. Of the total prescriptions, the majority of the promethazine was dispensed for oral formulations. Focusing on single-ingredient oral promethazine, dispensed prescriptions declined approximately 19 percent from 11 million prescriptions in 2012 to 8 million prescriptions in 2016.

We now move on to prescriber specialty data for hydrocodone-acetaminophen. Primary care

providers such as family practice, general practice, internal medicine were the top prescriber for hydrocodone-acetaminophen products followed by mid-level practitioners and dentists.

Using another data source, we assessed possible concurrent use of hydrocodone-acetaminophen, and promethazine products based on prescription claims data. In this analysis an episode of concurrency was identified when a prescription for hydrocodone APAP overlapped with the days' supply for a dispensed prescription for single-ingredient promethazine. Patients with overlapping therapy days of at least 1 day from both prescriptions were identified as patients on concurrent therapy.

This analysis of prescription claims data showed that hydrocodone APAP and promethazine were dispensed together. The number of patients with concurrent prescription claims declined over the study period to approximately 1.1 million patients in 2017. However, based on prescription claims data alone, it is not clear if the prescriptions

were prescribed together intentionally or for what indication.

In order to understand prescribers' intent, we used an office-based physician survey data source to explore intended use of hydrocodone-acetaminophen and promethazine together as well as diagnoses associated with the use of these products.

This figure provides the nationally estimated number of times hydrocodone-acetaminophen was mentioned during the office visit either to be used alone or concomitantly with another drug. Approximately 63 percent of reported use was for hydrocodone APAP to be used alone followed by hydrocodone APAP mentioned along with ibuprofen or cephalexin. No data was reported for the concomitant use of hydrocodone APAP and promethazine in 2016.

Using the same data source, this figure captures the most frequently mentioned drug for the treatment of nausea and vomiting as reported by the physician survey data in 2016. The most frequently

mentioned drug associated with diagnoses code for nausea and vomiting was ondansetron followed by single-ingredient promethazine.

As with all studies, there are limitations. Only outpatient utilization was assessed. No inpatient or mail order data were included in our analyses, however, this setting accounted for the majority of utilization. As mentioned, the concurrency data derived from prescription claims may be written from two different prescribers and for different indications other than OINV. For example, promethazine may be prescribed to treat nausea and vomiting associated with chemotherapy or HIV treatment.

The concomitant prescribing and diagnoses data based on survey data are not linked to dispensed prescription data. These data were derived from surveys of office-based physicians and may not have captured prescribing patterns of physicians who practice in other settings of care such as hospice, pain, cancer, or urgent care clinics. Our finding also does not include data

from prescribers such as dentists and mid-level practitioners. It may not be representative of all prescribers.

In summary, outpatient retail utilization of both hydrocodone APAP and single-ingredient promethazine products decreased during the examined time period. Concurrent prescription claims for hydrocodone APAP and promethazine has decreased over the study period to an estimated 1.1 million patients in 2017.

Based on survey data, hydrocodone APAP and promethazine-containing products were not reported to be prescribed together by the same prescriber during the same office visit in 2016. The most frequently reported drug for treatment of nausea and vomiting was ondansetron. Although mentions of promethazine were substantially lower, it was the second most mentioned drug used for the treatment of nausea and vomiting after ondansetron.

That concludes my presentation. Thank you. Now, I'll turn it over to Dr. McAninch for our next presentation on postmarketing data on misuse and

abuse of hydrocodone and promethazine. Thank you.

FDA Presentation - Jana McAninch

DR. McANINCH: Good morning. My name is Jana McAninch. I'm a medical epidemiologist in the Office of Surveillance and Epidemiology, and I'll be discussing the postmarketing data on misuse and abuse of hydrocodone and promethazine. First, I'd like to provide a bit of background and explain the purpose of this presentation.

In July 2017, the National Academy of Sciences, Engineering, and Medicine issued the report, Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. One of the aims of this report was to advise FDA regarding actions it could undertake to balance the needs of pain patients and the need to address opioid misuse.

The report recommends developing a regulatory framework that balances individual need for pain control with considerations of the broader public health consequences of opioid misuse to ensure that opioids are safely prescribed and that

as actually used, the drugs provide benefits that clearly outweigh their harms. The purpose of our review and of this presentation is to provide descriptive postmarketing data on hydrocodone and promethazine to help conform the consideration of Hydexor's risk-benefit balance.

Just a couple of definitions before we move to the data, there is often some confusion around the meaning of the terms "misuse" and "abuse" and the definitions vary according to the data source. Unless otherwise specified, I will use the following definitions consistent with other FDA communications.

Abuse refers to the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect, and misuse refers to the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse.

First I'll present some data on hydrocodone misuse and abuse. These data are from the 2016

National Survey on Drug Use and Health's large, annual, nationally representative household survey of individuals age 12 years or older in the United States. In 2016, an estimated 55 million people, or 20 percent of this population, had used a hydrocodone product in the past year, and approximately 7 million, or 2.6 percent of the population, had misused hydrocodone in the past year.

Misuse in this survey is defined as use in any way not directed by a doctor, including use without a prescription of one's own, using greater amounts more often, or longer than told to take a drug, or in any other way not directed by a doctor. Based on these data, approximately 13 percent of past-year hydrocodone users age 12 years or older misused the product in the past year. In the 18- to 25-year-old age group about 1 in 4 hydrocodone users reported misusing the drug.

In this survey, most of those who reported misusing prescription opioids reported that they did so to treat physical pain, with only about

12 percent reporting misusing them to feel good or to get high.

These figures show data collected from individuals in the U.S. who are entering or being assessed for substance use disorder treatment in the NAVIPPRO ASMIV surveillance network. In this published study, Cassidy and colleagues found that IR hydrocodone combination products were the most commonly reported drugs abused in the past 30 days. However, after adjusting for the number of prescriptions dispensed in the study coverage area, hydrocodone's abuse rates were the lowest of the opioid categories examined.

Next, these data are from our analyses of calls to U.S. poison control centers. From 2010 to 2016, there were a little more than 100,000 calls to poison centers indicating intentional exposure to a hydrocodone-acetaminophen product. Of these, approximately 12 percent were classified as abuse and 14 percent as misuse. Only 31 percent of the intentional hydrocodone-acetaminophen exposures were single-substance exposures, meaning that only

one drug product was involved. And of these, approximately 13 percent were classified as abuse and 23 percent as misuse.

Next are data from the NEISS-CADES project, which is a joint effort of the CDC, the U.S. Consumer Product Safety Commission, and the FDA that collects data on clinician diagnosed drug related adverse events in a national stratified probability sample of approximately 60 hospital emergency departments.

In 2016, NEISS-CADES surveillance activities were expanded to encompass emergency department visits resulting from abuse, self-harm, drugs used for unknown intent, and assault, in addition to therapeutic adverse drug events. In 2016, there were 73 cases in the NEISS-CADES sample corresponding to an estimated 5093 emergency department visits in the United States due to abuse of a hydrocodone-containing product. In 30 of these cases corresponding to 2075 visits nationally, hydrocodone was the only drug implicated.

There were also an estimated 3365 visits for therapeutic misuse of hydrocodone, for example, taking a very large amount to sleep or taking someone else's prescription medication; and 8287 visits where the intent of drug use was not known, for example, the patient may have been unconscious or unwilling to describe why the drug was taken.

These are data from analyses that we conducted of the drug involved mortality linked data files, which combine data from the National Vital Statistics Mortality files with information extracted from the death certificate literal text. From 2010 to 2015, there were approximately 20,000 deaths involving hydrocodone among individuals age 12 years and older. In approximately 1600, or 8 percent, of these, hydrocodone was the only substance mentioned, and approximately 39 percent of hydrocodone-involved deaths explicitly had misuse or abuse mentioned on the death certificate.

In 2016, FDA reviewed epidemiologic data on the route of abuse for hydrocodone combination products. We found that the route of abuse

patterns vary widely depending on the population being studied. Abuse of hydrocodone combination products is predominantly oral in all populations examined, but intranasal abuse is also quite common in some populations, particularly in those with more advance substance use disorders. However, the intranasal route is generally not reported as the preferred or the exclusive route for abuse of these products.

As far as harms, case series show that intranasal drug abuse can cause nasal tissue necrosis and fungal infections, but the incidence of these complications is unknown. The available data suggests that injection abuse of hydrocodone combination products is very infrequent.

I'll now transition to postmarketing data on misuse and abuse of promethazine, both alone and in combination with opioids. These data are somewhat more limited, and we're not aware of any national survey data on promethazine misuse or abuse.

First, let's look at the poison control center call data. From 2010 to 2016, there were

approximately 15,000 calls for intentional promethazine exposures. Of these, approximately 10 percent, or 1451 calls, were classified as abuse and another 10 percent were classified as misuse.

There were 570 abuse and 855 misuse calls in which only a promethazine-containing product was mentioned. Of these, there were 233 abuse calls and 450 misuse calls involving a single-ingredient promethazine product and 207 abuse calls and 231 misuse calls involving promethazine-codeine combination products. Approximately 30 percent of the single-substance calls involving promethazine-codeine products were classified as abuse and 33 percent as misuse. We also identified 79 abuse calls and 85 misuse calls involving both promethazine and hydrocodone-acetaminophen.

Within the 2016 NEISS-CADES sample of hospitals, there were 18 emergency department visits related to abuse of a promethazine-containing product, one case of therapeutic misuse and 8 cases in which the intent of drug use was not known. Of the abuse cases,

10 involved single-ingredient promethazine and 8 involved promethazine-codeine cough syrup. There were 4 abuse cases, 1 misuse case, and 3 cases with unknown intent where a promethazine-containing product alone was implicated. Case numbers were not large enough to generate reliable national estimates for these case types.

Our analysis of the drug-involved mortality link database found that from 2010 to 2015, there were 1696 deaths in the U.S. in persons age 12 years or older involving promethazine. In only 24 of these, or 1.4 percent, was promethazine the only drug mentioned. Approximately 35 percent of promethazine involved deaths were specifically flagged as involving misuse or abuse.

Multiple published studies have described abuse of promethazine-codeine cough syrup known by names such as "purple drank" and "lean." Abuse of cocktails containing promethazine-coating cough syrup was popularized in the 1990s by a number of rap artists primarily in the Houston, Texas area. Small surveys suggests that this practice is quite

common in some specific population subgroups and regions, but much less so in others.

In an interview-based study of injection heroin users in Vietnam, 75 percent of participants reported promethazine use in conjunction with heroin injection and described using promethazine to augment a suboptimal heroin dose or predosing in anticipation of impending withdrawal. Most stated that they disliked the actual effects of promethazine, including occasional hallucinations.

In a separate study of patients in methadone maintenance treatment in San Francisco, 26 percent of patients had urine samples that tested positive for promethazine. Only 15 percent of those with promethazine detected in their urine had an active prescription for promethazine. The study authors also noted anecdotal reports from their own clinical practice of promethazine use by methadone maintenance patients to potentiate the high from methadone.

Finally, we conducted an informal search of internet drug abuse discussion forum posts to

gather anecdotal information on how some people who abuse opioids talk about concomitant use of promethazine. This was an exploratory and purely qualitative exercise. What we found was that opinions appear to vary regarding whether promethazine enhances the experience of abusing opioids. Some individuals emphatically stated that promethazine enhanced their euphoria when abused with opioids; in this post, the individual noting use of promethazine as an opioid-sparing strategy. Some noted other desirable effects of promethazine, including sedation and relief of nausea and itching, whereas still others stated that promethazine sedative effects were undesirable when abusing opioids to achieve a high.

All postmarketing data have limitations, and I'll just mention some key limitations of each of the data sources that we used. First, the national survey data are limited by potential misclassification or misidentification of products and by potential non-response bias. Poison control center call data only capture misuse and abuse

events if the exposure resulted in a call to a poison control center. The fraction of events captured is unknown and may vary across time or products, and unattended out-of-hospital deaths are unlikely to be captured. Although the system is constructed to capture information on specific drug products, products can still be misidentified.

Emergency department visit surveillance data only include cases that result in a visit to an emergency department and do not result in death before or during evaluation. The quality of the data depends on the completeness and accuracy of medical record documentation.

The drug involved mortality data rely on death certifier mentions of drugs on the death certificate. The likelihood of investigating and reporting specific drug involvement varies across jurisdictions and over time, and misuse and abuse may not be explicitly mentioned even when they occurred, so these data likely represent an underestimate.

As in the national surveys, data collected

from people entering or being assessed for treatment or other enriched samples also have potential for misidentification of drug products, and these data come from non-representative convenient samples, so generalizability is limited. Internet drug abuse discussion forum postings have many limitations. Our search was not systematic. Again, misidentification of drug products is possible. There is no way to verify information and rumors or hearsay are sometimes reported.

In summary, as is true for all opioids, the overall risk-benefit balance of Hydexor includes potential harms associated with misuse and abuse. Hydrocodone is widely misused and abused often in combination with other drugs, resulting in thousands of calls to poison centers, emergency department visits, and deaths each year. However, relative to their very large prescription volume, hydrocodone combination products appear less likely to be abused than most other opioid products.

Hydrocodone combination product abuse is predominantly oral, however, in some populations,

particularly those with more advanced substance use disorders, intranasal abuse is fairly common although not generally the preferred or the exclusive route. Based on the available data, injection abuse of hydrocodone combination products is quite infrequent.

The postmarketing data indicate that promethazine is also misused and abused to a lesser extent than hydrocodone and usually in combination with opioids or other drugs. Poison center and emergency department visit data as well as the published literature indicate that abuse and misuse occur with both single-ingredient and combination promethazine products, including promethazine codeine cough syrups.

Anecdotal data suggests that some individuals who abuse opioids believe promethazine enhances the opioid abuse experience through euphoric, sedative or other antiemetic or antihistamine effects, whereas others do not find promethazine's effects desirable when abusing opioids. Thank you.

FDA Presentation - Ellen Fields

DR. FIELDS: Good morning. My name is Ellen Fields. I'm the deputy director in the review division. I'm just going to provide a summary of the FDA presentations and try to put them into context for the questions you'll be asked to discuss later.

You've heard a number of presentations from both the agency and the applicant, and there's been a lot of overlap, and there are most areas where we actually agree with the sponsor, so I'll try to point those out.

All the data taken together are intended to inform the discussion about not only are there benefits and risks in the intended patient population, but also the risk-benefit balance that considers the broader public health implications surrounding the misuse and abuse of opioids and their associated consequences.

Dr. Wong presented information on drug utilization, and we learned that hydrocodone-acetaminophen combinations are the most

frequently prescribed outpatient opioid analgesic in the country. Outpatient utilization for hydrocodone-acetaminophen combinations as well as single-ingredient promethazine products have decreased.

Based on claims data, concurrent prescriptions for hydrocodone-acetaminophen combinations and single-ingredient promethazine has decreased. Based on data from office visits, no mentions of concomitant prescribing for hydrocodone-acetaminophen and promethazine by the same prescriber were noted. We also know that ondansetron was the drug most frequently mentioned for the treatment of nausea and vomiting in the outpatient setting, and that was followed by promethazine.

Dr. Jiang presented both the efficacy and the safety, and we're in general agreement with the applicant regarding all these findings. Hydexor was evaluated in two phase 3 studies in patients prone to or anticipated to experience nausea and vomiting with opioid administration. Replicated

data demonstrated analgesic effectiveness of Hydexor and efficacy compared to hydrocodone-acetaminophen for the prevention of opioid-induced nausea and vomiting. As Dr. Jiang said, we believe the indication should specify just the prevention of OINV in patients prone to nausea and vomiting and not reduction.

Again, we agree with the safety findings from the applicant. We noted typical opioid related adverse reactions from Hydexor and an increase in CNS related adverse events compared to Norco that were most likely related to the promethazine, and these were predominantly drowsiness and lightheadedness and did not result in any serious consequences.

Again, regarding the human abuse potential study, we generally agree with the findings from the applicant. Just to reiterate, because promethazine is included in Hydexor and it has a number of CNS effects on its own, we requested that the applicant conduct a human abuse potential study to evaluate the abuse potential of adding the

promethazine to the combination as compared to hydrocodone-acetaminophen alone.

The human abuse potential study conducted with Hydexor showed there were no statistically significant differences in positive or negative subjective responses when Hydexor was compared to hydrocodone-acetaminophen using doses of hydrocodone that were equivalent to 3 and 5 times the recommended 7.5-milligram therapeutic dose of Hydexor. Hydexor did produce a statistically significant increase in drowsiness compared to hydrocodone APAP suggesting that promethazine produces an additional degree of sedation. However, this effect did not appear to influence the abuse potential of Hydexor.

The data from this study support the conclusion that there are no differences in the abuse potential of Hydexor compared to hydrocodone-acetaminophen, and thus the presence of promethazine in Hydexor does not alter the abuse potential of the drug product as measured in this controlled study environment. And as with other

hydrocodone-acetaminophen products, Hydexor will be placed under Schedule II of the Controlled Substance Act if it is approved.

As you just heard from Dr. McAninch, we need to look at potential harms associated with misuse and abuse when evaluating the overall risk-benefit balance of opioids. Hydrocodone is widely misused and abused often in combination with other drugs, resulting in thousands of poison center calls, emergency department visits, and deaths each year. However, relative to the very large prescription volume, hydrocodone combination products appear to be less likely to be abused than most other opioid analgesics.

Hydrocodone combination products' routes of abuse are predominantly oral, and populations with more advanced substance abuse disorders, intranasal abuse is very common but not necessarily the preferred or exclusive route, and injection of these products are infrequent.

Misuse and abuse of promethazine and opioids occur together, and anecdotal evidence suggests

that some but not all individuals who abuse opioids believe promethazine enhances the desirable euphoric effects of opioids as well as sedative effects. However, the available epidemiologic data are not informative as to whether Hydexor is more likely to be abused or misused than currently marketed hydrocodone-acetaminophen combination products or whether promethazine CNS depressant effects add meaningfully to the risk of overdose and death associated with opioids when misused or abused concomitantly.

In conclusion, Hydexor appears to be safe and effective in the proposed patient population with some increases in CNS effects compared to hydrocodone-acetaminophen alone. Hydexor is not intended to be an abuse-deterrent formulation, and that's the same as all of the other marketed and approved hydrocodone-acetaminophen combination products that are on the market.

The human abuse potential study demonstrated no difference in abuse potential compared to hydrocodone-acetaminophen alone in that control

study, and epidemiology data and postmarketing anecdotal information showed there may be some use of promethazine with opioids to enhance their effect when abused, and these were mostly for cough products.

If approved, Hydexor will be indicated for use in patients prone to OINV and will be under Schedule II of the Controlled Substance Act and will be subject to the classwide opioid REMS. We'll be asking the committee to consider all these data as you discuss the overall risk-benefit of Hydexor as it relates both to the intended patient population as well as the broader public health impact.

I want to thank Dr. Lloyd who helped me put these slides together but could not be here today, and that's it. Thank you.

Clarifying Questions

DR. McCANN: Thank you.

Are there any clarifying questions for the FDA or FDA speakers? Please remember to state your name for the record before you speak. If you can,

please direct questions to a specific presenter. Dr. Meisel?

DR. MEISEL: Thank you. A question for Dr. Wong. The data on the utilization of the combination products, do you have that broken down at all by dose, 5 milligram, 10 milligram, 7 and a half milligram? Is that available at all?

LCDR WONG: Hi. Thank you for the question. For our presentations, we did not. We just did analysis. But we are not aware of any evidence that shows that the 7.5-milligram strength is the most frequently dispensed of hydrocodone APAP products. We're wondering if the sponsor can provide that data to show that.

DR. MEISEL: So there are no prescription data that differentiates that? You're not able to pull that?

LCDR WONG: Yes.

DR. McCANN: Dr. Litman?

DR. LITMAN: Thank you. I have a couple of questions for the sponsor, please. If you could bring up slide CS-6.

DR. McCANN: It's just for the FDA right now. We're going to get to the questions --

DR. LITMAN: Oh, I'm sorry.

DR. McCANN: -- later.

DR. LITMAN: Sorry about that.

DR. McCANN: So we'll go on to Dr. Raghunathan.

DR. RAGHUNATHAN: Thank you. In the sponsor's provided data, did FDA look at the difference in the use, amount used, in the two treatment groups? Is that an issue of more compliance in the Hydexor group compared to the Norco group? Do you have the data on looking at the use in this particular study population?

DR. HERTZ: I'm not completely clear what you mean by compliance.

DR. RAGHUNATHAN: So amount of drug used, did they use all the dispensed drugs in the two groups? Do you have the data on that?

DR. HERTZ: The two efficacy studies were inpatient studies, and I'm not sure if we have that --

DR. TRAVIS: We took a look and we didn't see any -- James Travis, statistician. We didn't see any differences in the level of use between Hydexor and the Norco treatment groups in the clinical studies. They used about the same number of tablets over the 24 or 48 hours, that they used as the primary efficacy period.

DR. McCANN: Dr. Michna?

DR. MICHNA: I was just wondering why FDA did not require human abuse liability studies in the clinical dosing. The reason why I ask is this whole controversy of people exposed to short-term opioids then evolving into a misuse and abuse scenario. Maybe at a lower dose of opioid versus promethazine there might be a difference, and I was just wondering why that wasn't required.

DR. HERTZ: In these studies, it's necessary to give enough product for people to have the euphoric effects, desirable CNS effects, and 7.5 milligrams of hydrocodone is not especially reinforcing. I'm going to ask Kit Bonson from the controlled substances staff to comment as well.

DR. BONSON: Good morning. I'm Kit Bonson. I'm on the controlled substances staff. The reason that we don't do those assessments in the patient populations is because the measures have not been validated in a patient population. So we always use people who have experience with these drugs, whatever class of drugs we're assessing, in an abuse context, and presumably, patients do not generally have that.

DR. MICHNA: I understand that, but the question is with promethazine, maybe that would be different. We're not just looking at a regular opioid study. We're looking at a psychoactive, euphorigenic-dysphoric combination of drugs, and that's the reason why -- it's not your typical opioid study.

DR. HERTZ: Right, but at the higher doses, we couldn't meaningfully differentiate the effects. So you're suggesting that at the lower doses there might have been some sensitivity, but if people aren't even getting the positive psychoactive effects at all at the lower doses, then it's going

to be hard to distinguish an effect of promethazine.

DR. MICHNA: Right. But this is a surrogate for patients, right? And I understand the complexities. My issue is that I'm worried about the evolution of patients; is this more euphorigenic in the clinical dose to a patient? And I'm not sure -- I understand the limitations, but I'd like to have seen some reasoning why that would not be something to worry about.

DR. HERTZ: I'm going to borrow Dr. Comer from the sponsor or at least ask if she has any insight on this.

DR. COMER: I understand your question and I understand your concern, but I completely agree with Dr. Hertz, actually, because the most appropriate population to test are the recreational opioid abusers, so they've had a lot of experience with taking opioids and getting high from them. And they typically use much higher doses on the street than what are prescribed.

So testing a dose of 7 and a half milligrams

in someone who is abusing opioids will likely result in very small euphoria related effects like liking or getting high. So it would be hard to separate out anything because you're in a floor effect.

Does that answer your question?

(Dr. Michna nods yes.)

DR. COMER: Okay.

DR. McCANN: Dr. Morrato will be the last question for the session.

DR. MORRATO: I just wanted to have a follow-up clarification for Dr. Raghunathan. I may not be pronouncing it correctly. I think the question around adherence or compliance, one of the presumed benefits of having a blister pack and so forth is that ultimately patients need self-limit and take less pills. So is there any evidence from the clinical trials program that that in fact is what happened? That made me also think, the dosing in the clinical trials, were blister packs being used or just regular pill administration?

So we really don't have the evidence. And

there may be a difference between study 002/003, which are the safety/efficacy, and then 006, which is the actual-use study in osteoarthritis, which went out for 2 weeks.

DR. HERTZ: I don't think the blister packs were used in any of the clinical trials. And in terms of accounting for the amount of drug return, we saw that in the applicant's slides, that showed there was very little drug unaccounted for during the clinical trials.

DR. MORRATO: Unaccounted for could be I took 2 pills and I returned 8, and it's all accounted for versus I took 8 pills and returned 2. I can't remember what you presented, but I think it was like you accounted for the pills, or was it really looking at how many pills did they have to take over that period of time? Maybe it's a sponsor clarification.

DR. SMITH: Right. Thank you. Tom Smith with Charleston. First was the idea of drug accountability, and as you saw, there were a lot of pills given to the patients and we had a very high

return rate. Again, from the experience that Dr. Comer mentioned as well, the experience with other Schedule II opioids, this was actually a very high return rate, so that provided a level of confidence.

With regard to was there a difference in the number of pills taken per day, the 006 study, it was roughly 2.6 on average, is what patients took for those 14 days, and then in the 002 and 003, somewhere around 3 and a half once they were an outpatient, and that was similar to what they took with Norco for pain.

DR. MORRATO: So there was no differential difference in returning of the number of pills or doses between the two arms. Is that correct?

DR. SMITH: That's correct.

DR. McCANN: So we're now going to take a 10-minute break. Panel members, remember there should be no discussion of the meeting topic during the break among yourselves or with any member of the audience. We will return at 10:20. Thank you.

(Whereupon, at 10:10 a.m., a recess was

taken.)

DR. McCANN: Before we get started with the open public hearing, Dr. Staff would like to give some clarifying information about the epidemiology of promethazine.

DR. STAFFA: This is Judy Staffa from OSE. With regard to Dr. Michna's question about the prescription volume for hydrocodone combination products and what percentage are the 7 and a half milligram as opposed to the 5 milligram, we ran some very preliminary data, and basically about half the prescriptions for hydrocodone combination products are the 5 milligram and about 20 percent are the 7 and a half, just to clarify that.

DR. MICHNA: [Inaudible - off mic].

DR. STAFFA: There's also a 10 milligram and a 2 and a half milligram.

Open Public Hearing

DR. McCANN: Thank you. This is the beginning of the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for

information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it 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 relationships 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 for your travel lodging or other expenses in connection with your attendance to the meeting.

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

The FDA and this committee place great

importance on the open public hearing process. The insights and comments provided can help the agency and its committee in their consideration of the issues before them. That said, in many instances and for many topics, there are a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way -- and respect, therefore please speak only when recognized by the chairperson. Thank you for your cooperation.

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

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

conflicts of interest. I think we all agree that opioids need to be held to a high standard of approval because of their risks as well as high rate of misuse and abuse. Please consider these questions as you evaluate Hydexor.

Should the FDA approve additional conventional opioids? Commissioner Gottlieb has stated that the FDA's response to the opioid crisis includes shifting the opioid market from one dominated by conventional opioids to one dominated by opioids with meaningful abuse-deterrent properties. Since Hydexor does not have these abuse-deterrent properties, it would not fit this goal.

Should the FDA approve drugs that combine an opioid that causes unpleasant side effects with a drug to counter these same side effects? The novelty of Hydexor is that it combines hydrocodone with a drug to prevent nausea and vomiting caused by hydrocodone. This can encourage patients to take the drug and continue relying on it.

Commissioner Gottlieb recently warned the

public about the abuse of loparamide, a drug that prevents unpleasant side effects of opioid withdrawal. Since Hydexor contains a drug component that prevents unpleasant side effects, it too has a high potential for abuse. Does it make sense to approve Hydexor given this added potential for abuse?

What does the human potential study and the postmarketing data tell us about how this drug would be used? The human abuse potential study only looked at oral administration. It did not test the abuse potential of other routes such as snorting or IV. In addition, it is not clear if there would be a difference in preference for users who experience nausea and vomiting.

Hydexor uses a version of promethazine with faster bioavailability, which could make it more likely to be abused. But the bottom line is there are reasons to be very concerned about the abuse of this drug, and the studies don't give us enough information to counter-balance these concerns.

It is also difficult to predict how a

Hydexor would be used in a clinical study. Not all patients need an anti-nausea drug when they take hydrocodone, however, if heavily promoted, and we know that it's likely, Hydexor could be prescribed by doctors to help patients to avoid nausea they wouldn't necessarily have experienced. This would expose many patients unnecessarily to adverse events resulting in the addition of this drug.

Is the drug safe for older adults? The safety data indicate that patients taking Hydexor were more likely to faint and/or fall, however, only a small number of patients 65 and older were included in the clinical trials. Older persons are especially susceptible to drugs that call sedation or drops in blood pressure, and this drug has two active ingredients that can potentially cause dangerous cumulative effects. These drugs were not studied enough in patients over 65 to determine how risky it might be for them.

Does the sponsor's proposed mechanisms for reducing risk for misuse adequately address the potential? The sponsor proposed 3, 5, and 7-day

packaging to reduce prescribing large amounts. However, these packages are based on 6 pills a day while patients took an average of 2 to 3 pills a day during the as-needed portion of the trials. If the clinician expected a patient to use 15 pills over the course of the 5 days and prescribed a 5-day pack, the patient would still have twice as many pills as they were expected to take. This could encourage patients to take more pills.

The proposed return program could be a great option to remove unneeded opioid pills, however, we do not have enough data on how well it would work or whether patients and caregivers would use the program, therefore we cannot count on it. As you know, many patients keep old prescriptions, especially pain pills, just in case, and this contributes to misuse and abuse by patients and family members.

In conclusion, consider how this drug fits into the context of the drug market and how it is likely to be used and misused. Do the benefits outweigh the risks of putting another conventional

opioid on the market when designed to treat its own side effects and are the attempts to reduce excess pills sufficient?

Opioids provide a benefit and harm towards society. As advisory members, please advise the FDA to carefully and cautiously consider the potential for abuse for this opioid. Thank you for your time and consideration of our views.

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

DR. LORENC: Thank you. Good morning. Can I have 7 minutes? Because I was allotted 7 minutes, please, on the timer. Thank you so much.

Good morning. My name is Paul Lorenc. I'm a board certified esthetic plastic surgeon practicing in New York City, practicing at Lenox Hill Hospital as well as in a fully accredited office, operating in my office. I'm representing

my practice and most importantly my patients. I have over 20 years experience in a very busy clinical practice. I'm very active academically with multiple publishings, publications, and book chapters. I also take part in clinical research and have been involved in well over a dozen of phase 3 clinical trials mostly dealing with botulinum toxin type A and also medical devices.

I'd like to thank you for allowing me to share with you my clinical perspective on the importance of opioid-induced nausea and vomiting in my patients. Why is it important especially in plastic surgery patients? Because in 35 percent of my patients, postoperative nausea and vomiting is prevalent and it has serious consequences. This is in line with what's out in the literature as far as OINV, which is rated at 40 percent.

Nausea and vomiting is consistently reported in my patients as one of the most important aspects of the overall procedure. Marcus [ph] reported in PRS, one of our main journals, that 73 percent of unscheduled readmissions to the hospital, in our

patient population, are secondary to nausea and vomiting. These are patients who have already recovered in the recovery room. They have been discharged from the hospital or from ambulatory surgery centers like mine, so these are patients who are free of nausea, they are taking PO, and well hydrated. But 73 percent of them are readmitted because of nausea and vomiting.

This obviously has severe consequences not only returning to the OR, another anesthetic exposure, but certainly the costs associated with it. And probably just as important, patient satisfaction because, as you know, in plastic surgery, patient satisfaction, how it's scored and perceived by the patient, is critical basically in our existence.

Also, there's an estimate by Marcus that an ambulatory surgery unit can lose up to $2 million in income per year because of the possible readmission and dealing with the postoperative nausea and vomiting. So as I mentioned, specifically in our patient population, it's

critical. And it's mostly critical in patients where wide undermining of the tissue is done, such as patients who undergo facelifts, abdominoplasty, or breast augmentation, because if that patient develops nausea and vomiting and is wretching, blood pressure goes up and there's a significant increase in hematoma, which might necessitate again and return to the operating room.

So why is it so important specifically in plastic surgery? It's simple, because my patients are those patients at high risk. Apfel, as you mentioned before, came up with a scoring system, a 4-point scoring system, of who is more prone to postoperative nausea and vomiting or opioid-induced nausea and vomiting? These are my patients. Ninety-one percent of my patients are women, and these women are 3 times more likely to develop opioid-induced nausea and vomiting. One of the other factors is non-smoking. I don't operate on smokers. This is elective surgery, so again, another factor in my patient population.

Lastly, opioid use. I routinely prescribe

hydrocodone 7.5 milligrams to my patients for postoperative pain control. So if you score these patients, according to Apfel, there's a 61 percent chance of postoperative nausea and vomiting in my patient population. If you include on top of that a surgical predictor, which is the length of time in the operating room, which seems to be triggered at 90 minutes, that's 100 percent of my patients basically. So it's very important in my patient population to be careful and to really be concerned about post-opioid use and nausea and vomiting.

I'd like to briefly share with you a patient who underwent in my office -- a 52-year-old patient who underwent a facelift and a blepharoplasty, uneventful, and was discharged from my office 8 hours afterwards after taking 7.5 milligram hydrocodone with acetaminophen. She incurred intractable nausea and vomiting, which necessitated readmission. She was treated of course with Compazine without any effect.

I had to admit that patient to Lenox Hill Hospital for IV hydration and blood pressure

control because typically my patient would have nausea and vomiting. They get anxious; blood pressure goes up. There's a higher incidence of hematoma formation in patients who are hypertensive. So this patient ended up being admitted to Lenox Hill Hospital for hydration, electrolyte imbalance correction, and observation to make sure that she did not develop hematoma. And there's a factor that's always in the background, which is the cost that's incurred not only by the patient but by the hospital and possibly even by their healthcare provider.

So as far as OINV in plastic surgery, it has huge consequences. As I've mentioned to you before, if a patient develops a hematoma after their blood pressure rises when they are wretching, because of this specific type of surgery that we do as plastic surgeons, it can have tremendous consequences. And the severe consequences include hematoma evacuation, which again necessitates a return trip to the OR, and just importantly another exposure to an anesthetic, which can again cause

more postoperative nausea and vomiting. It can cause wound dehiscence, aspiration, and respiratory compromise.

Lastly, specifically in plastic surgery patients, patient satisfaction is the most important factor that patients look at as far as their overall experience.

So is there a need for a combination therapy such as this, hydrocodone, acetaminophen, and promethazine? In my opinion there is because you have shown -- I have seen this morning -- that there's decreased incidence of opioid-induced nausea and vomiting, therefore their recovery will be quicker, and avoidance of possible return to the operating room, and hematoma evacuation is more predictable in that way.

So I think overall it's a very important aspect to consider to benefit my patients. And lastly, I just want to thank you for allowing me to share my clinical perspective of the importance of opioid-induced nausea and vomiting, especially how it relates to a surgical practice such as mine.

Thank you.

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

MS. MALLICK-SEARLE: Good morning. My name is Theresa Mallick-Searle. I'm a nurse practitioner. I've been doing acute and chronic pain management for over 10 years. I work at Stanford University Medical Center, Division of Pain Medicine. I was asked to be part of this program today by Charleston Laboratories. I was paid to come and was put up at the lovely Hilton overnight last night, but I have no financial interest in the outcomes of this study.

I would like to start by sharing a brief story that will hopefully educate you as much as it educated me, something that personally happened to me. About three years ago, I was attending a meeting in Philadelphia not unlike this, and I was unexpectedly hospitalized. During that hospitalization, I was offered opiates for

analgesic relief of pain, and unexpectedly and unfortunately I developed nausea and vomiting myself. This was associated with under management of my pain for the most part because I chose not to use the opiate provided for me because of the alternative of the unpleasantness of the vomiting and nausea.

You've heard a lot today by many speakers about the incidence and occurrence of opiate-induced nausea and vomiting. I'm here to share my personal and clinical experience with you. As a nurse practitioner in the specialty of pain management, I have a familiarity with opiate-induced nausea and vomiting, but it wasn't until I experienced it that I really perceived and felt the unpleasantness and the suffering that goes along with opiate-induced nausea and vomiting to the point of choosing not to use the opiates that I needed for my analgesic pain relief because of the alternative, and then unfortunately a delayed recovery and a 7-day hospitalization.

I took it upon myself after this experience

to go back to my institution and query my staff and my colleagues about their understanding of opiate-induced nausea and vomiting and their understanding of the patient suffering associated with it, and it wasn't much better than mine, unfortunately.

So last year, I took it upon myself to think about how I could best go and educate my peers as well as colleagues nationally about this incidence, patient suffering, and what we need to do to improve. So I published a journal article, and it talked about the importance of the recognition, the management, and ultimately to decrease patient suffering. And what I found was pretty consistent in the review of the literature as to what you've heard today, that the incidence of opiate-induced nausea and vomiting with exposure to an opiate was about 40 percent nationally, and about 50 percent of those individuals had the unfortunate experience of vomiting as well.

We additionally found that patients were disinclined to report their incidence of opiate-induced nausea and vomiting to their healthcare

provider similar to the underreporting of opiate-induced constipation, those unpleasant side effects that the patients refuse to tell us about. We found that several studies also showed that patients were willing to endure more pain and less pain relief other than foregoing the pleasantness of opiate-induced nausea and vomiting. And finally, that patients that were experiencing opiate-induced nausea and vomiting had increased ED visits, surgical complications, and postoperative provider visits.

In closing, we're a profession of healthcare providers because we want to improve our patients' lives. We need a simple, predictable, evidence-based way to identify our patients that are at risk for opiate-induced nausea and vomiting and manage these side effects appropriately when the requirements of using a short-term opiate to treat acute pain aggressively is called for. Thank you for your time.

Clarifying Questions (continued)

DR. McCANN: The open hearing portion of

this meeting is now concluded, and we will no longer take comments from the audience. We now have some time for some clarifying questions to the sponsor, and we're going to start off with Dr. Higgins.

DR. HIGGINS: This is in follow-up to Dr. Morrato's question. I had the same question regarding the Hydexor return campaign. I have questions about whether the sponsor has made forays with state level departments of public health. For example, in Massachusetts, we are now discovering there's a problem with the CVS kiosks that are proposed to be used for returning medications. We have medication assistance programs that are unwilling to accept that as a possibility.

So there are some difficulties at the state level in making these things happen. I'm just wondering -- I did hear that there is some conversation with DEA, and I'm just curious if there's any forays with state departments of public health.

DR. SMITH: We have not met with the various

state departments at this point. But yes, we realize those are conversations that we will have to have. We have been seeking a lot of advice as to how does the patient return and where do they return product to. So again, we're exploring all of those at this time.

DR. McCANN: Dr. Litman?

DR. LITMAN: Thank you. I wanted to ask about, in your packet, slide CS-6. It's a comparison of all the side effects. And thank you for putting the placebo because I don't feel like I'm the only one who has all these every day.

One of the things I noticed -- and it's not in the slides, but it was in the packet -- is that in this particular study, in 002 and 003, even though you could take a maximum of 12 pills a day, the patient in these studies only took around 3 or 4. What I would love to see is a comparison, the same slide there, but of those patients that actually took on the higher side. And I don't know if you have that data readily available, but it's got to be there somewhere, and I would advise the

FDA to look at those.

Each pill of Phenergan -- sorry, promethazine -- is 12 and a half milligrams, and that's potentially -- there's not going to be that many patients that take 150 milligrams a day, but I guess it's possible. Those are the real patients that I want to see this slide, not the average.

DR. SMITH: I appreciate your question. There's by the number of doses. And again, these were actively solicited, and I think, again, it speaks to the incidence with regard to -- this is any opioid related symptom, any of those 9 symptoms that we discussed. But again, they were fairly equal between the Hydexor and placebo groups across the number of doses.

DR. LITMAN: Thank you.

DR. McCANN: Dr. Porter?

DR. PORTER: Thank you. I'm referring to CS-22, the commitment to responsible use. It says in here that you are planning on a commercial audience of selected surgeons and acute pain specialists, but they are only about 10 percent of

the subscribers for opioids. Most of the subscribers, according to the FDA's graphic, is family practice, general practice, internal medicine, nurses, nurse practitioners, physician assistants, and dentists. And by leaving out that group, you're ignoring the people that are most likely to prescribe this drug.

So I just wanted to know why you decided that surgeons -- and it says selected surgeons and acute pain specialists -- especially if this is short acting because short actings are usually given not by necessarily pain specialists.

DR. SMITH: Right. Thank you, Dr. Porter. We really feel that the need for this product is in that select audience. We believe there are roughly 1.7 million registrants with the DEA, and we believe we're looking at maybe 1 to 2 percent even at top-market penetration. So we're looking at 15[000] to 20,000 prescribers, so we're looking at those select surgeons. We're looking at surgeons like the gentleman in the audience, plastic surgeons, maybe OB/GYN surgeons, patients who would

be having that acute pain, that limited acute pain that we're speaking about.

To your point, anyone who can prescribe a Schedule II could prescribe Hydexor. If we pick that up through our REMS and through our surveillance, we plan to try to educate them to make sure that they're using it in a safe and appropriate way. I think like any medication that a physician prescribes, they have to understand the benefits that it would provide versus the risk. And I think it also behooves them -- and I think most clinicians do -- to educate them about possible side effects.

DR. PORTER: My next question, who are you going to market this to or is this too early to talk about marketing? Commercials on -- just marketing. We'll leave it at that.

DR. SMITH: Again, we're very early in our planning. At peak -- I think, too, a nice way to think about this, Dr. Comer presented the IQVIA data. Do we have the IQVIA slide that shows trends? It was also provided by FDA. And

again -- I want to see that slide. We can show this one.

This is the slide that Dr. Comer presented, and FDA had the similar IQVIA data that shows that this is what's happened over the last six years. In 2017, roughly 180 million prescriptions were written for opioids in the U.S. Of that 180 million, roughly 80 million were for hydrocodone APAP products. And I believe that the rescheduling, the upscheduling of hydrocodone in 2014, helped further decrease that trend, so I applaud this change.

The thing that Dr. Comer spoke to is that the number of pills per prescription has actually gone up, so still what we're seeing in the marketplace are prescriptions of 60, 90, 100, 120 tablets. Of these 80 million, we believe that the market, if you will, is probably 1 to 2 percent at peak sales, and we're displacing that 1 to 2 percent. So hopefully we're contracting the market somewhat. It's a very small number. Also in our planning, we're thinking of somewhere in the

neighborhood of 75 to maybe 150 representative, tops, and that's kind of where we are in our plan.

DR. McCANN: Dr. Ruha?

DR. RUHA: Hi. Michelle Ruha. My question is for Dr. Schachtel about the trials. I'm concerned that the adverse effects that were reported in I think 002 and 003 and the various trials may not reflect what would be seen with real-world use. There's a lot of commonly prescribed medications that have antimuscarinic properties like antihistamines, antipsychotics, antidepressants, and muscle relaxers. There are so many antimuscarinic medications, and promethazine is antimuscarinic. Something I see in my practice is a lot of toxicity from the people being on multiple antimuscarinic mediation.

My question is, in those studies 002 and 003, exclusion criteria included use of any confounding and contraindicated products, and I don't think we were given exclusion criteria for the others at all. So I'm wondering were medications with antimuscarinic properties

considered confounding or contraindicated products for inclusion in the trials.

DR. SMITH: Dr. Schachtel?

DR. SCHACHTEL: Bernie Schachtel. Yes. I was going to say of course, but clearly we had to avoid any confounding because we wanted to focus deliberately only on the effects of the low-dose promethazine.

DR. SMITH: Maybe perhaps I can share a little more color on that. If I could have my core slide on 006. In study 006, the patient population wasn't addressed, and this study provided me, as a physician, with some extra confidence around an older patient population as well. The mean age was 61.

Again, 179 patients were enrolled and 97 percent of them completed the study. Here, other medications were allowed. They were taken off of -- so these were people who were not screened for being at risk of OINV. These were people who were opioid naive. These were people that their non-steroidals weren't sufficient in

treating their acute flares of OA. And the reason this study was performed was to get additional safety data.

This is the adverse event profile that we saw with, again, the agency pointed out drowsiness, lightheaded, dizziness, the second most common. And while it's rudimentary, we did take a look at hydrocodone APAP trials that have been done. We did a PubMed search and looked at 10 trials where there were 7 to 10-day studies. This AE profile is very similar to what's reported in those studies. And again, I understand that that's not an apples-to-apples comparison, but it gives me some increased confidence in those patients.

DR. McCANN: Dr. Choudhry?

DR. CHOUDHRY: I think this question is for either the sponsor or for the FDA. I'm interested in the dizziness and vital sign changes that were reported in these trials, 002, 003, and 006. In the FDA's briefing documents, they report drops in systolic pressures of about 9 millimeters of mercury for Hydexor as opposed to 6 for Norco and 2

for placebo. The relevance of those varies, obviously, based on context and where we are starting.

Do we have anything about absolute values, like what were mean pressures, for example, in this population?

DR. SMITH: I can start, and I welcome my colleagues from the FDA to step in. Do we have the chart that we made looking at hours?

Like the FDA, we were concerned about, again -- that's good. I'll project the slide for all of you. Like the FDA, we were concerned. We realize we're adding an alpha adrenergic to hydrocodone. Both labels, both the hydrocodone APAP labels as well as promethazine labels, under warnings and precautions have a severe hypotension warning, and Hydexor would carry that as well.

What you can see -- and again, this is consistent with the data that FDA provided in their briefing document as well. But what you can see is a higher percentage of patients in the Hydexor group versus the Norco group, which have reductions

in both systolic and diastolic, and they tend to start agreeing around 24 hours.

I should also report, I think, again, to look at this under context, this was expected, so again, we wanted to understand it as best we could. None of these patients went on to -- they all completed the studies. They did not have any dose reductions or discontinuations. None of these patients suffered syncope as a result of their blood pressure changes. And I had shown this slide -- actually I had not shown it in this four, but we'll go ahead and project it if we could.

In studies 002 and 003, there were three associated AEs reported as hypotension with Hydexor, 3 with Norco, one of which was rated as severe by the investigator, and then one with placebo. And again, all of these did not recur. Then in study 006, again, we had an older patient population. There were no AEs of hypotension that were reported.

DR. CHOUDHRY: That's helpful data. I'm just wondering if we have actually mean values.

What are the actuals? You're giving us binary values for what is low blood pressure perhaps by conventional criteria, but I'm still curious about where the pressures are beginning and where do they end.

DR. SMITH: We don't have it in a slide format.

DR. McCANN: Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff here, and I have a few clarifying questions. First, for Dr. Smith, just to drill down a little bit more on what the meaning is of selected surgeons and acute pain specialists, based on your answer before, it seems to not be clear as to the selected surgeon that you'd be marketing to, has been clarified yet. Is that correct?

DR. SMITH: We haven't drilled down as to who and where. That is correct.

DR. ZACHAROFF: Okay.

DR. SMITH: But again, that could be -- there's a variety of surgeons. There's the oral maxillofacial surgeons and so forth. But it

would be those patients where obviously that benefit is needed to prevent some of the complications that we heard of.

DR. ZACHAROFF: Right. So then it might be more appropriate to refer to the surgeons who are operating on patients in a high-risk category like the plastic surgeon mentioned.

DR. SMITH: Correct.

DR. ZACHAROFF: Who is an acute pain specialist? I'm interested to know.

DR. SMITH: You know, there are people who -- and they are. To Dr. Porter's earlier question, there are people who are in primary care -- and that would be a small number -- who have a special interest in how do you effectively treat those people with acute pain. One of the nice things that we think, particularly around our packaging, is that something that hasn't been happening is that whole patient-physician dialogue. There are those physicians who want to know after 3 days, and 5 days, and 7 days are you still having pain, and if not, is the pain due to something

else.

DR. ZACHAROFF: It seemed like in the majority of your studies, and certainly in reviewing the background briefing materials, that certainly the focus was on post-surgical pain patients. It seems to me that that patients who suffer acute pain versus post-surgical pain patients may or may not be the same in many cases.

Just so I'm clear, are we really talking about the patient that we should imagine in our minds as a patient who's a post-surgical patient and the surgeon is very concerned or the anesthesiologist is very concerned about experiencing OINV, or are we thinking about office-delivered care where patients are being treated for an acute pain situation that's likely to be limited for 14 days where OINV is a concern. Which is it?

DR. SMITH: I'm going to ask Dr. Gan to give it a little more color. Dr. Zacharoff, you're right. These are tried and true pain models -- the bunionectomy, the oral surgeons -- that have been

used now for a couple of decades, but we needed those to show both the efficacy of the pain as well as the OINV. But this type of acute pain and pain associated with OINV is not necessarily a surgical limitation. But again, Dr. Gan being a clinician, I'd appreciate his perspective.

DR. GAN: I'm an anesthesiologist. I'm not a primary care physician. So I'm going to tell you in my area how I'm going to use this drug potentially. Imagine a scenario where you treat a patient for the surgery and this patient throughout in the recovery room. And you treat the patient, and the patient got better, and if it's a same-day procedure, the patient is going to go home. The patient's in pain and he or she had nausea and vomiting. Now she's afraid to go home just having a pain medication. This is where I think this product, which has analgesic and antiemetic together, would be helpful in my scenario.

DR. ZACHAROFF: So it reinforces the definition of the post-surgical model for sure. And just one last question, and this refers to

slide CE-9 where we talked about OINV as co-primary endpoint, and I believe it was Dr. Schachtel.

My question is, what was used as the rescue antiemetic in the cases where it was necessary? What was the agent used? And secondly, when I see that Norco was used as a comparator, should I assume that Norco was used with no antiemetic protocol being employed along with the Norco? Those are my two questions.

DR. SCHACHTEL: Bernie Schachtel for the transcriber. The antiemetic was at the physician's discretion. Because there's no antiemetic approved for OINV, we couldn't determine that there was only one that the doctor could use. Regardless, the drug of choice that was used most frequently was ondansetron, 4 or 8 milligrams orally.

We found, however, that many of the patients -- in fact, I don't know if I have the percentages here -- no, I don't. But I can tell you that many of the patients who were on the ondansetron, considerably more than the patients who were prescribed the ondansetron who were on

CO-108 [ph], required repeated doses. In fact, in the 003 study, which was 48 hours of observation, many of those patients who required repeated doses at the doctor's discretion of the ondansetron orally went on to require parenteral, again, ondansetron administration, 3 to 4-fold more than in the Hydexor group.

DR. ZACHAROFF: Okay. But Norco as a comparator in this study --

DR. SCHACHTEL: Did not.

DR. ZACHAROFF: -- was used as Norco without --

(Crosstalk.)

DR. SCHACHTEL: Exactly.

DR. ZACHAROFF: So you were comparing Hydexor, which has an antiemetic in its formulation, comparing it to a narcotic acetaminophen formulation without an antiemetic.

DR. SCHACHTEL: Right. And the reason for that was to determine the incidence of OINV in those patients who received just the emetogenic agent Norco, the hydrocodone, and not to

contaminate with another antiemetic. And as a previous question here, we wouldn't want to have any other antiemetic there at the same time.

DR. McCANN: We have about 10 minutes to complete the questions, so we're going to go on to Dr. Ciccarone.

DR. CICCARONE: Hi. Dan Ciccarone, UCSF. A question for Dr. Comer regarding study 007, the abuse potential study. I remain unconvinced from the briefing documents from industry and also I believe in conversation with the FDA about the sample size. So I need to be convinced a little bit more about why 40 subjects was adequate, was a power calculation done, et cetera.

DR. SMITH: Dr. Comer?

DR. COMER: Thank you for that question. I believe the sponsor conducted some power analyses post hoc and found that the sample size that they used was in excess of 95 percent power. In the studies that I performed and a lot of other academics that I've spoken to, our sample size for similar types of studies examining the abuse

liability of opioids used sample sizes on the order of 12 to 15. And in all of the studies that I do, those sample sizes also have greater than 90 percent power to detect reasonable differences in effects. I wasn't involved in this study when they calculated the sample size, but just from my own experience, that's a pretty large group of people.

DR. McCANN: Ms. Robotti?

MS. ROBOTTI: Thank you. A question on the packaging. Do you have a clear slide showing the packaging so we can actually read the words on it? CS-19 seems to be the clearest that we've seen, but do you have a better one?

DR. SMITH: I don't believe we do, no. No, ma'am.

MS. ROBOTTI: Can you bring it up?

DR. SMITH: Yes, ma'am.

MS. ROBOTTI: The reason I point it out is because I don't see -- what I do see on it, I believe, are 3-day pack, 5-day, 7-day pack, the 3-day pack having 18 samples. The packaging looks

like what I would imagine the Z-Pak looks like, or I know a Z-Pak looks like, where you're encouraged and in fact told and ordered to use every single pill in it. So this looks like a product you should use every single pill. It says it's to be used in 3 days or to use it all in 5 days, or to use it in 7 days. But I don't see where it says use only as needed, don't worry about having leftovers.

Does it say that somewhere on there? And if not, why not?

DR. SMITH: It would be on the prescription label to take one every 4 to 6 hours as needed for a maximum of 6 per day. We certainly can discuss with the agency, as we get to that point, about what is the appropriate wording that should be put on the package.

MS. ROBOTTI: Just to finish my thought, which ends up being a comment, I would urge the FDA to not put on a package that it is a 3-day versus a 5-day because it encourages the consumer, the patient, to think that that is a requirement to

finish it. That's really a comment. Thanks.

DR. SMITH: Thank you, Ms. Robotti.

DR. McCANN: Dr. Habel?

DR. HABEL: My question actually was a follow-up about the target population. Just for clarification, I'm kind of wondering, the population that you chose for the actual-use study, is that a population that you would also be targeting when you commercialize it? Because that's not really a post-surgical population. Would that be in a pain specialty?

DR. SMITH: No, ma'am. That would not be -- oftentimes, people who have osteoarthritis, it's a chronic pain condition, so that would not be a target for this product. This is to be used in acute pain and to provide that immediate care. So that is not a target population.

DR. HABEL: So you chose that population more just to demonstrate safety, but not because you thought it was going to be an actual-use population itself?

DR. SMITH: To get additional safety data on

the products; yes, ma'am.

DR. McCANN: Dr. Arfken?

DR. ARFKEN: Yes. My question is about postmarketing. For those of us who talk to heroin users either clinically or out in the field, we know that there are some who use heroin even though they experience nausea and vomiting. However, the concern here is people who might have a barrier to using opioids at all because of that and now they're exposed to it. I was just wondering what part of the postmarketing surveillance would address then continuing on to use and then to abuse opioids, especially when they would probably transition to a cheaper source such as heroin and getting promethazine in another way.

DR. SMITH: Thank you. I'm going to try and answer both of your questions using a couple of our experts. I want to first let Dr. Comer again speak around the fact that these patients, despite the reduction of nausea and vomiting, at those higher doses, there did not seem to be any increase in abuse. And then I'm going to ask Dr. Novak to come

up and talk a little bit as well.

DR. COMER: Can I have slide CA-10 in the backup slides? I completely understand your concern, and that's one that I share with you. I work with heroin abusers routinely, and I actually have a NIDA-funded study where we're giving naloxone out to drug users in an attempt to help them rescue their other co-users. So I recognize that it's a massive issue and it's something that keeps me awake at night.

But one thing that makes me feel somewhat reassured from the data that I reviewed that the company has is -- this is the time course of drug liking with the different conditions that were tested. We just want to draw your attention to the broken orange circle and the open blue square. Those were the two higher doses that were tested, so that's what you'd be worried about.

I know from working with this population for a long time that the rate of onset of drug effects, of drug liking and high, are critical for its abuse potential as well as the maximum effect that's

produced, so both the Tmax and the Cmax, and the fact that the time-effect curves were right on top of each other were really reassuring to me. And I feel like -- and these were including people who experienced the nausea and vomiting in both conditions, and it was less with Hydexor, but the euphoric effects were the same. So I don't think that the abuse liability of the Hydexor is in excess of what's already out there.

DR. SMITH: Dr. Novak?

DR. McCANN: Dr. Galinkin?

DR. GALINKIN: I also have concerns about the packaging as well because it really does imply, I think, that patients should be taking 6 pills a day for 7 days. And since that is the case, did you look specifically if there was sedation that got worse over time for patients who took it for your maximum duration of 14 days, 6 pills per day? Were the side effects worse? I mean, the drug is a 17-hour -- you do have a drug with a 17-hour half-life, so does that accumulate over time and does that worsen sedation over time?

DR. McCANN: Who's going to answer that?

DR. SMITH: I will. I'm sorry. I was just having the team pull up a slide. I apologize. We did look at what happened to these symptoms and these adverse events over time. As you can see, they did decrease over time. Again, this is from studies 002 and 003. Your question specifically was around study 006, and I'll show you this one as well, and this is what happened to drowsiness over time.

DR. GALINKIN: Were the patients taking 6 pills per day, each of the patients taking 6 pills per day?

DR. SMITH: No, sir, they were not. As I shared with you earlier, when you looked at the overall adverse event profile, though, it was very similar to what we currently see with marketed hydrocodone APAP with regard to the incidence of drowsiness. But no, sir, they weren't.

DR. McCANN: Thank you. That concludes the questions to the sponsor. Right now, we're going to hear from Dr. Sharon Hertz who will provide us

with a charge to the committee.

Charge to the Committee - Sharon Hertz

DR. HERTZ: Lots of questions, lots to consider. We're going to request that you provide your opinions, your advice, based on your expertise and experience, to help us find a reasonable and responsible path forward.

Our questions I'm just going to summarize. You'll be seeing them shortly. But we're going to ask you if the program supports the safe and effective use of this product for the indication: prevention of opioid-induced nausea and vomiting. We're going to ask you if you have specific concerns about it not being an abuse-deterrent formulation. And we're also going to ask about concerns that you may have about greater risk in the sphere of misuse and abuse. And then ultimately, based on these considerations, whether you feel the product should be approved. Thank you.

Questions to the Committee and Discussion

DR. McCANN: We will now proceed with

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 first question we're going to deal with is question number 1. Does the applicant's clinical program support the safe and effective use of Hydexor as an analgesic and for prevention of opioid-induced nausea and vomiting that is limited to use in individuals likely to experience OINV? Open for discussion.

Dr. Higgins?

DR. HIGGINS: I have considerable concern, as was expressed by one of the public speakers, about the data for older adults, 65 and up. I know that there is some discussion from the sponsor that the mean age was 61 for one of the studies. I just feel like there needs to be more data on that population in particular given the less tolerability to these medications as people age and the greater prevalence of surgeries that would

require the use of this kind of product.

DR. McCANN: Dr. Choudhry?

DR. CHOUDHRY: I have concerns as well. I think the side effects that we have seen are predictable, so there's nothing here that's surprising or strange. But because they're predictable, the question then becomes whether or not putting them in combination so they can predictably occur is a good idea or not. So it makes me think that there is really two ways forward.

Either you say forget it; you can't do this in combination -- the 20 percent diastolic less than 60 is a lot, leaving aside the sedation drowsiness data that we've seen -- or you are very restrictive to whom this is given. And I think the broad indication, which we'll get to later, of patients with acute pain as opposed to those predominantly in the postoperative setting, high risk of post-op nausea and vomiting with very clear contraindications, it's really one of those two options. I think for me, as was offered earlier,

the idea of forcing combinations sometimes is exactly forcing us the wrong way and reduces clinical flexibility.

DR. McCANN: Dr. Ciccarone?

DR. CICCARONE: I'll pass.

DR. McCANN: Ms. Robotti?

MS. ROBOTTI: Hi. First a question. It's an FDA slide question, Dr. Timothy Jiang, and I apologize if I'm saying your name wrong, slide 9, severe AEs. It says -- and I'd like to point out -- "number of subjects with at least one severe OSS on Hydexor is 50 percent and 33 percent for days 1 to 2 and 3 to 5 versus Norco 35 percent and 22 percent days 1 to 2 versus 3 to 5."

Can I add those percentages or do they duplicate each other? I'll ask the doctor.

DR. HERTZ: These don't distinguish individual patients. You can't necessarily add across cells.

MS. ROBOTTI: Okay. Then as part of my comment, I'd like to point out that I think 50 percent as a severe opioid-induced symptom is a

number we should take seriously. It's a lot higher than 35 percent on Norco.

Also, I'm concerned about giving this medicine prophylactically to anybody who might feel nauseous. As a woman, I get nauseous on long elevator rides; forget boats. I am of the age in this study, although I don't tell anyone, and I've never smoked. So if I was going in for bunion surgery, check-check-check, I would get this product. But I was given opioids in the early '90s for back pain -- let's not even go there -- and was on it for 29 days. Let's not go there either. Never felt nausea the entire time.

So I would be given this drug -- I would be given three drugs instead of two. I would be given promethazine. I would be exposed to all the risks of increased drowsiness, lowered blood pressure, respiratory depression, promethazine's unique side effects of dizziness -- well, constipation isn't unique -- ringing in the ears. I would be at risk of all of that for no reason.

So for that reason, if this drug were to get

approved, I would suggest a label indication should not say to prevent but only be in response to somebody who has had a bad reaction in the past or is having a bad reaction now. It's a period of time, and I'm sorry that people would be uncomfortable. And I recognize that there are going to be some surgeries where the risk of being overmedicated is better than the risk of vomiting, but that's a very small amount. So please don't do that.

After reviewing the documents and listening to the presentations today, I don't find this drug offers any benefit by combining all three drugs. You could give promethazine prophylactically before the drug if you have a history, if you have a problem with it. There's no need to limit the ability to tailor the dosage and the drug to an individual's need. That's it.

DR. McCANN: Thank you. Dr. Meisel?

DR. MEISEL: Thank you. I'm going to echo a lot of what Dr. Robotti said, although I'm not a woman and didn't have some of these experiences you

had. The question on the table here is, does the benefit of this drug offset the new risks, and I'm having a really hard time with this.

First of all, it was stated originally that 1 out of 5 people who get a prescription for Vicodin walk out of the pharmacy, take a pill, and throw up. That's preposterous. That just isn't the case. This is a hyper-enriched population that's very prone to this sort of a problem. It excludes the real-world situations that were described before with people who are on other drugs that are anticholinergic and what have you, and there are an awful lot of people who are on an awful lot of those kinds of medications. We do decrease some nausea with this, but at the expense of a number of other adverse events, blood pressure and all that sort of stuff.

Promethazine is a nasty drug on its own; it really is. And there's a reason that the data that the FDA showed about antiemetics that are being used is predominantly ondansetron. And there's a reason that ondansetron is selected, is because,

yes, it's got some problems and may not work the same way, but it doesn't have the adverse event profile that a drug like promethazine, or Compazine, or some of those other drugs have.

So when you think that we're going to expose everybody who needs Vicodin or Norco to another drug, promethazine, to me that's adding an awful lot of risk for relatively little value. For the situations where you know somebody gets really urpy and has got a real problem with narcotics, there's nothing to stop you from giving a second prescription for ondansetron, or promethazine, or whatever for that particular situation. That's available to everybody today. We don't need to put this into a combination product and add those risks for everybody.

DR. McCANN: Dr. Zacharoff, please.

DR. ZACHAROFF: Kevin Zacharoff. I just want to clarify the question at hand, that it's asking the question without the inclusion of the proposed indication that Hydexor is indicated when alternative treatments for pain are inadequate,

because that implies to me that other agents have been tried prior to the indication for Hydexor.

DR. HERTZ: The way we have the indication laid out for the opioids is when other products are inadequate, or are expected to be inadequate so that you don't have to run everybody through -- like for instance, post-op, you don't have to give everybody acetaminophen followed by an NSAID, followed by this before you get -- if you're coming out of the OR, one can get you up to something stronger. But that's sort of mixed in, and it will be in the language.

DR. ZACHAROFF: Okay. Because the wording, I do personally believe in the ability, and I have relied on for many years, to predict the likelihood of somebody being at increased risk for opioid or postoperative nausea and vomiting, as Dr. Gan mentioned, and there's a lot of credibility there. But again, as we just heard from Sharon, I would not consider it to be indicated after alternative treatments have been tried because I'm empirically going to prescribe it for someone if I think

they're at increased risk. Thank you.

DR. McCANN: Dr. Michna?

DR. MICHNA: Yes. I just want to get back to the inflexibility here. Here we have an indication, this postoperative pain that needs to be very flexible, and we're proposing a drug that has no flexibility. Then I have to think of what the clinical reality is. If people are having side effects, the doctor's going to say cut the pill in half, yet we have no clinical data to show that that's effective. In the same sense, we're using 7.5, which I believe is at least a little bit higher dose than usually given. And then if that's not effective, instead of going to a 10 milligram. we're going to a 15 milligram, and again, we have no data on that.

So I think this lack of flexibility is really causing me to look at this in a negative light, especially for such an indication that by its nature, it needs a flexible solution.

DR. McCANN: The sponsor would just like to clarify.

DR. SMITH: And I probably should have been clearer earlier, again, as to why the dose was selected. We wanted to have a product that would benefit the majority of patients with acute pain in that immediate setting. Also, by choosing this 7 and a half, the maximum that could be taken a day is 6. So 45 milligrams versus if we used a 5 milligram, 60 milligrams. So we're limiting the hydrocodone dose, and we showed that it was effective for pain.

The promethazine, I heard a lot of conversation around the promethazine combination. As you all know, currently both labels caution against using with one another. And what I hear from physicians is, "I don't know how to prescribe them, Tom." We know from IMS data that about 10 percent of patients who are receiving immediate-release opioids are co-prescribing -- within a few days period anyhow if not on the day of the procedure, are co-prescribed promethazine. And what I'm hearing from physicians is, "I don't know what to tell to take, Tom. Do I tell them to take

1 to 2 of their opioids? Do I tell them to take the promethazine before the opioid? Do I tell them to take it with the opioid?"

So I have my patients self-titrating pain, but also self-titrating now their antiemetic. So that's why we believe that the fixed dose in this instance does help those patients who require an opioid and also are at risk for OINV.

DR. MICHNA: The problem is that in clinical reality, there's a spectrum of patients. Not everybody is one dose fits all. And what you're saying is contrary to the clinical realities. What's going to happen is patients are going to take two of these and maybe three of these. And just by saying it's limited is not -- so the patient's going to run out, and with all these dose-limiting insurance programs, if the practitioner wants to prescribe an additional prescription, because of this hard wiring, it's going to be rejected by insurance in an acute situation. By the time it's all settled and done, that patient potentially would have a period of

several days of being excess pain.

So again, post-op pain needs flexibility, and what you're proposing for that indication is not flexible.

DR. HERTZ: I need to interrupt. We need to have the committee talk now rather than -- I just want to hear from the committee now please.

DR. McCANN: Dr. Bateman?

DR. BATEMAN: I share a lot of the same concerns that have been raised by the other panelists about the risk of exposing patients to drowsiness, confusion, syncope, and lower blood pressure when the promethazine is being added in a prophylactic fashion for the patients who experience nausea and vomiting. But I'd also like to bring up the potential risk of respiratory depression.

In our briefing materials, the label for Phenergan was included, and there's a warning about the risk of fatal respiratory depression associated with its use and recommends avoiding it in patients with compromised respiratory function that might be

at heightened risk. There's more and more literature coming out about the risk of overdose in patients that are co-prescribed opioids and other sedatives or other drugs that cause respiratory depression like benzodiazepines and gabapentinoids.

I know in the trials that were done with about a thousand patients, they had no cases of respiratory depression, but it's a rare side effect, something that you would not see in a trial of a thousand patients where most of the patients were exposed for relatively short durations but a potentially catastrophic complication. So I think that's a risk that we also should keep in mind in weighing the buy of this drug.

DR. McCANN: Dr. Morrato?

DR. MORRATO: I also agree with many of the safety concerns, so what I wanted to add to is thinking about how this might then translate to how we evaluate in a postmarketing setting. I agree with Dr. Choudhry, it's hard to understand whether or not what we're seeing is the effect of seeing the two drugs, and our comparison is being forced

to a drug that's just the one drug. So is the difference really true when it's out in real-world practice or not? And we don't really have, I think, that evidence to say, well, if the one drug is being used with an anti-nausea drug in real world, maybe those safety profiles look more similar.

I think I applaud the FDA on really trying to understand what is the utilization patterns existing and what can we learn. It's disappointing that we don't really have that drilled-down data in the decision-making, so I'm even now more disappointed that the sponsor didn't present, if you have, information from physicians around here's how they're thinking about addressing this problem, why that wasn't systematically collected and not just anecdotal because it gives me pause on the ability to really evaluate the safety profile if this drug is in market and whether or not we're seeing safety signals teased out by how it might be utilized or not.

So these questions around are we overdosing,

are we now forcing profiles together of two different drugs, it's going to get lost in the background noise of these are common side effects. So that gives me pause as well of how do we think about even evaluating postmarketing and if we're seeing a similar experience to what we see in these trials.

DR. McCANN: Dr. Raghunathan?

DR. RAGHUNATHAN: This question calls for lots of balancing acts and somewhat a paucity of information to make that balancing act. In the Norco group, if almost everybody got some antiemetic medicine, then it makes sense saying that, well, they're getting it anyway, whether this is an alternative way of giving 1 pill rather than 2 pills.

I agree that I think this loses the flexibility of tailoring the medication use to different people, but at the same time I'm trying to see whether there is a significant section of the population for which this will be a reasonable way of prescribing an opioid when you have the

opioid-induced vomiting as a really big thing for them.

So I think this is a question of is this universally applicable, or restrictions have to be applied on how this is prescribed, and for whom it is prescribed. I'm trying to find out from these data, really, can we identify for whom this can be prescribed and whether this could be useful.

DR. McCANN: Are there any more comments on this question? Dr. Porter?

DR. PORTER: Thank you. The inflexibility of the prescriptions is a concern for me and the fact that it's not titratable and that each of the pills has a set amount of promethazine and also of the hydrocodone. I think once it's FDA approved, even if it's approved for this small little area of people, once it's out there, then it's going to be available to everyone, and that's my concern; that we can say who it should be approved for, but once it's out, it doesn't matter because it's going to be available and it's going to be used by everyone. And if the marketing is to the public, which I

don't know what the rules are now about opioids -- but if the marketing is to the public or to general practitioners, then it's going to look extremely appealing.

DR. McCANN: Dr. Zacharoff?

DR. ZACHAROFF: Kevin Zacharoff. Playing on what Dr. Michna said, in a real-world setting, there is going to be a subset of patients who have breakthrough pain if this is prescribed as directed, and there's been no discussion about what would be provided for these patients in the event that they have breakthrough pain and how they would take it. My concern would be that somebody might tell them, well, you're only supposed to take a maximum of 6 of these a day, so then the question becomes what will I recommend that they do if they have breakthrough pain?

Again, I'm worried about these acute pain specialists and what decisions they might make. But I would think that in some subset of patients, there would have to be co-prescribing of this medication with some other medication in the event

that pain breaks through because I would not want the patient to double up on doses of this medication.

DR. McCANN: I would like to just briefly summarize some of the comments here. I think they come down to both safety concerns and philosophic concerns. The safety concerns that were brought up were concerns about data for older adults. There's just not enough of that; concerns about predictable although adverse effects such as blood pressure, and just because a drug is known to cause hypotension doesn't mean that it's good that it causes hypotension; and concerns that patients may treat their pain, titrate the drug to their pain, and unintentionally overdose on the promethazine. Those would be the safety concerns.

Philosophic concerns that came up were basically that forcing combinations and fixed doses may not be a good idea, ever, for any medication, and also the concern that we just don't have enough data to know if the benefit of forcing this combination would outweigh the risks.

Now I would like to go on to question number 2 for discussion. There are currently no immediate-release hydrocodone-acetaminophen combination products with abuse-deterrent properties that are approved and are on the market. Do you have concerns that Hydexor does not have abuse-deterrent properties?

Dr. Litman?

DR. LITMAN: Thank you. As of today, the published literature does not indicate that abuse-deterrent formulations are making any kind of an impact. They may in the future. The studies, they're beginning. So as of today, then no.

DR. McCANN: No. Okay. Dr. Galinkin, please.

DR. GALINKIN: Since this combination, particularly the codeine-promethazine, was widely used for this purple drank thing, I don't see why you would release something that you could dissolve essentially in a glass of whatever and make essentially the same product. Since hydrocodone is a metabolite and structurally very similar to

codeine, it seems to me that you'd have a product with high-abuse potential in that population, which wasn't looked at, which has a non-deterrent property, which dissolves easily in anything.

DR. McCANN: Ms. Robotti?

MS. ROBOTTI: Thank you. I find the study on abuse potential unconvincing given that the participants in the trial were recreational users of opioids. These are people who presumably are not opioid naive. They know if they're going to have discomfort from it, and they either don't have discomfort or they don't care about that. The liking scale showed of course they liked it only as much as the HC-APAP.

Out in the real world, my guess would be that those people who have avoided opioids because it gives them stomach upset would not have to and would be able to party with that drug and have a new whole gateway into drug use this way, just to use a very strong word. I think that they'd find it a significant benefit to allowing them to use the drug.

Secondly, I question Charleston Lab's commitment to this mitigation at all given that the packaging encourages around-the-clock use of the drug, with the exception of the unexplained Hydexor buyback program, which has not been explored on any level and is some vague promise that they've plenty of time to have conversations about. And they have no idea if they can deliver on this promise at all on a legal basis.

They promise an independent risk mitigation advisory board some time in the future. Why would Charleston Labs not convene the board now when they're developing the risk mitigation plan if they truly want the input of a independent risk mitigation team? I'm not convinced that this drug won't be abused, and I'm not convinced that this company won't do everything they can to stop that abuse.

DR. McCANN: Dr. Ruha?

DR. RUHA: Michelle Ruha. I don't really have concerns either that it doesn't have abuse-deterrent properties; one because I'm not

sure they make a difference, I agree; and two, because it will be dispensed in these packages as it is rather than large quantities.

DR. McCANN: Dr. Ciccarone?

DR. CICCARONE: Dan Ciccarone, UCSF. I'll leave my larger comments around the potential abuse of this drug for the next question. But just in terms of the ADF question, there's not a lot of evidence for crushing, snorting, and intravenous injection of hydrocodone combination products, nor promethazine. So actually for this particular question, I do not have a lot of concern.

DR. McCANN: Dr. Kotz?

DR. KOTZ: I am an addiction psychiatrist who sees opioid-use disorders in patients every day, so I personally do not have concerns about these abuse-deterrent properties because the fact is anytime you take any opioid, there is some risk. So if we're trying to evaluate does this have more or less I think in terms of the information we've been given, it doesn't have any more likeability, but you can never be certain of that.

So for me, it's looking at this as one option, and I'm not concerned about the abuse-deterrent properties in this particular medication.

DR. McCANN: Does anybody else have any comments that they would like to make?

(No response.)

DR. McCANN: I'd say that there's a slight preponderance of people that suggested that abuse-deterrent policies have not been demonstrated yet to be effective, so the fact that there may not be a very strong abuse-deterrent program in place here may not make any difference.

Several members were concerned that this drug did have abuse potential by dissolving it in drinks and that there may be a population of individuals that would have suffered with OINV that now would not, and they may be at higher risk for developing addiction problems. Other people commented that the mitigation plan was not well formulated and that that needed to be formulated before they would be in favor of this drug.

Let's go on to the third question. Epidemiologic data suggest that misuse and abuse of promethazine, either alone or in combination with opioids or other drugs, have resulted in emergency department visits, contact with poison control centers, and deaths. Please discuss whether you think Hydexor poses greater risks than currently marketed hydrocodone-acetaminophen products.

Dr. Choudhry?

DR. CHOUDHRY: There are two parts to this question, really. One is about misuse and one is about risk, and the two go together but not necessarily. And I'm going to return to this idea that there are predictable side effects here, and when taken to a real-world population, who now we add in other antimuscarinics that were discussed and other antihypertensives, and anything else which has CYP interactions, I think we open ourselves up to a much broader risk profile than we're seeing in these small studies.

We see this consistently for drugs as they go to market across classes. In this case, we see

signal even in small selected studies. So I think, at least from the perspective of the second part of this question, whether or not this poses greater risks than the currently marketed products, I think the answer is yes.

DR. McCANN: Dr. Meisel?

DR. MEISEL: I agree, particularly in the misuse element of this question. Abuse, I'm not quite so sure. But there's no doubt -- I think it was described before, that, yes, 1 tablet every 4 hours, but some people will take 2, and some people will take 3, and some people will take the entire box at 1 dose, that sort of thing. That's going to happen in terms of misuse. And when that does happen, because it's not a question of if, it's a question of when, it's going to increase the risks of these folks ending up in the ED with all sorts of nasty adverse events that otherwise wouldn't have occurred had they'd been on plain hydrocodone-acetaminophen.

DR. McCANN: Dr. Litman?

DR. LITMAN: Thank you. When I was

preparing for this meeting and I was reading through a lot of the material, I had the exact same thoughts, so I did some research and found a couple papers that looked at the effects of promethazine, big overdoses. And I found a couple, and I'm happy to share them. But I was quite surprised that the toxicity was not as I expected. One that came from Australia, the mean amount ingested -- and these are like purposeful ingestions -- it was 650 milligrams. Another one comes from the U.S. and had something similar from poison control center data.

Clearly, there will be an increase in side effects, and yes, there may be an increase in emergency room visits for delirium, or drowsiness, or anticholinergic effects, as was discussed before, but I was surprised that the serious toxicity that I thought I would find was not there.

DR. McCANN: Dr. Zacharoff?

DR. ZACHAROFF: Kevin Zacharoff. The thing that concerns me with respect to the risks as opposed to currently marketed

hydrocodone-acetaminophen products rests on what I consider insufficient information regarding the risk mitigation strategies. I have to discount the return program because the details of it don't seem to exist yet.

So since I don't know what it is and we weren't able to clarify what it is, I can't consider that to be something that I would consider. I also think the lack of true stratification about who the prescribers might be and who the recipient patients might be makes it troubling for me as well.

DR. McCANN: Dr. Ciccarone?

DR. CICCARONE: Dan Ciccarone. My expertise is in heroin misuse and consequences, so I'll present from my experience and my read of the literature. I was quite familiar with the San Francisco studies on methadone maintenance patients having illicit, let's say, promethazine in their urines as well as studies on chronic pain patients that both came out of San Francisco General Hospital.

Promethazine is a minor drug of choice among some. We do see promethazine misuse both with low-potency opioids, for example, codeine, as well as high-potency heroin and methadone. The use of this I believe is because it does potentiate the nod. There's a mixed opinion about what the nod is. It could be the high levels of euphoria; it could also be just deepening sedation. Either way, the user's experiencing something they want, a potentiation of this thing called "the nod." We've seen this for a couple of generations now.

Now having said that, do I think that this is going to lead to wide-scale misuse and abuse? It seems unlikely. I mean, it's low levels of promethazine in this product. I applaud the FDA's research looking at drug forum data. Even though it's qualitative and limited in many ways, it does bring out some of the richness of user experience, both positive and negative. A lot of people don't like promethazine in combination with their opioids.

I do also appreciate industry's approach

here as part of the panel that discussed dose-limiting packaging. I do think they have a first-in-category packaging product here. I do share the concerns about it being used for compelling patients to feel like they have to use 3, 5, and 7 days. I think that could be corrected. But the idea of limiting the number of patients exposed to this, limiting the number of dosages that go out into the world, the packaging group believes strongly in that, and I think I applaud industry for bring that product forward.

So I'd say unbalanced low levels of risk, but there will be some. There will be some misuse and abuse of this, and probably in a prescription linear level with the amount of prescriptions that go up. But I think low level also in terms of severity of outcome, in terms of deaths and severe consequences like hospitalizations. Thank you.

DR. McCANN: Dr. Kotz?

DR. KOTZ: I didn't realize I hadn't put my sign down, but I agree with everybody that I think that the return program, even though it's a great

concept, I think that that would be very, very hard to implement. But I also agree that the packaging can be changed, so it says, with the prescription, that you can use this PRN. You don't have to use the whole pack.

The reality of it is people with addicted disorders are going to use perhaps as many as there are there, but they would do that, too, with pills in a bottle in which we saw the data showing that even though the number of prescriptions for hydrocodone have gone down, that the amount of pills that a person receives in that one prescription has gone up dramatically. So I think that at least there is a finite number in the package, and that can be somewhat helpful.

DR. McCANN: Dr. Ruha?

DR. RUHA: Michelle Ruha. I agree. I don't think promethazine itself really poses much of an increased risk. Even if someone was to overdose on the entire package, they're more likely to die from opioid toxicity than promethazine. Promethazine itself isn't a huge problem.

But I'm more concerned -- I do think that Hydexor poses greater risk than just hydrocodone-acetaminophen only because it can result in so many additive or drug interaction effects, not only the cytochrome P450 interactions and the antimuscarinic ones, but it does prolong QT. I think there was a comment earlier that it doesn't, but it does prolong QT. So if somebody was on other QT prolonging drugs, I think there's a lot of opportunity for potential drug interactions. So I do think it's increased risk over the currently marketed product.

DR. McCANN: Dr. Morrato?

DR. MORRATO: I'd like to comment from a public health or population level kind of risk. Having sat on committees like this, probably over 15 of them or more, reviewing deterrent formulations early in the process, and now we're seeing some data, reviewing and being part of the rescheduling, you can see how the impact of some of these decisions sort of play out in the larger market. And it really from a public health

standpoint made me really think that it's a very complex, dynamic system of which we really don't know a lot of these interconnectedness and fully understand it.

So I now approach these kinds of questions more concerned about unintended consequences, even if they might be small effects at an individual level, how they play out at a population level and whether or not we might unintentionally be shifting a risk curve in the wrong direction given the overall epidemic that's happening.

For instance, I agree too that blister pack in of itself seems like the right direction. It's restricting the number of pills, et cetera, but with a fixed dose number of pills and might that actually end up into higher dosing in some patients. We saw data that was presented that the more you take, the more likely is your risk of developing dependency yourself, so, again, that overdosing kind of shifts the curve a little bit.

We didn't talk much about the education. I'm not a clinician, but it sounds like listening

to the clinicians around here, this combination is novel or maybe it's not used intentionally in practice because of concerns. So really, what is the education that might be specific to the product that's different from what is the REM general education around abuse and deterrence. Really, have we considered that background noise of risk communication and the nuance story that needs to happen with this drug?

Then I would agree with Dr. Galinkin. It may not be a large impact, but if it's making it easier for some to abuse it or think they're abusing it -- I know we've spent time on DXM, and that was only like 8 to 10 percent of teens trying it out and abusing it, and yet that was a significant problem when you look at it at population level. So again, you take this small risk and multiply it out by all of the general abuse.

We saw very limited data on discussion from the sponsor, I think, about thinking about how these market dynamics play, which makes me think

the fact that here we are at the stage of an advisory committee, and they don't know how they're going to commercialize the drug? In theory, this could be approved in days from these kinds of meetings. I find that quite concerning, in addition to the reasons that have been discussed around, really, the likelihood of seeing a takeback program or a buyback program really work.

So these things I'll just summarize. From a population level, it makes me more cautious. So really, unless there's real clear benefit, I'm starting to more likely err on worrying about the unintended consequences.

DR. McCANN: Dr. Raghunathan?

DR. RAGHUNATHAN: Trivellore Raghunathan. This question caused for me a comparison, what am I comparing with. If the currently marketed products are given with a separate drug, which contains promethazine, to account for the opioid-induced vomiting, then I think these are very similar risk factors in both groups. So it depends upon what is the extra drug that is given and what is the impact

of the extra drug that is given for the opioid-induced nausea and vomiting.

One thing that I think is because we are mitigating opioid-induced nausea and vomiting, that creates more use of this particular drug, then I think it can potentially lead to more misuse because they can use more. But I don't see that the alternative is clearly crafted, and we don't have data on that alternative on what would be the misuse properties of the alternative.

DR. McCANN: Are there any more comments?

(No response.)

DR. McCANN: I'll try to briefly summarize. First it was brought up there already is a risk signal from the very small studies that's been brought up and that once this is broadly marketed, that we could anticipate that these small risks would at least grow in numbers, and that could be something to think about, specifically drowsiness and blood pressure.

Although most of the committee anticipates that some of these side effects will be severe

enough to bring patients to emergency rooms and to the care of physicians, the majority do not believe that there's going to be a lot of serious side effects with the addition of promethazine to this drug combination. There also were concerns about the potential drug interactions, especially in older patients who are on many different medications.

The packaging was brought up again. The packaging as is appears that it may encourage some patients to take the entire dose, whether they really need it or not, but the limited amount of medication within the packaging may encourage less overall use of opioids, and that would probably be a good thing. People are not happy with the return program. It's just very, very briefly sketched out at this point, poorly characterized, so we can't really say too much about that.

The entire discussion today I felt were basic concerns about the particular drug combinations that were chosen by the sponsor, if we were to go with a combination, were these the right

combinations that we would choose as a pain specialist.

That is my summary. We will now go on to the voting portion. We will use an electronic voting system for this meeting. Once we begin the votes, 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 wish to change your vote, you may press the corresponding button once the vote is closed.

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

I think we're ready to do the vote. I have to read the question. Question number 4, should Hydexor be approved? If there are no questions or comments concerning the wording of this question, we will now open the question to discussion.

I thought we were going to vote first, but I guess we're going to discuss. Are there any questions on the wording of the question or anything like that?

(No response.)

DR. McCANN: All right. So then we can vote.

(Voting.)

DR. McCANN: Everyone has voted, and the vote is now complete.

DR. CHOI: For the record, we have 2 yes, 19 no, and zero abstentions.

DR. McCANN: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. And we'll start on my right side

or this side of the table.

DR. HABEL: Laurie Habel. I voted no. I thought that the efficacy was convincing, but I was concerned about the lack of flexibility in the dosing and the ramifications of that. So that was my main consideration when voting no.

DR. ARFKEN: Cynthia Arfken. I voted no. In addition to what was stated, I was concerned about the postmarketing surveillance and all the plans for it. I also am concerned about how it would be approved, the indicator. I think to really show effectiveness, it should be shown comparable or superior to a PRN approach to doing it with two medications.

DR. ZACHAROFF: Kevin Zacharoff. I voted no, and my main reasons were the logistics in a clinical sense, pre- and post-prescription. There was no discussion about whether prophylactic measures could be taken and what would happen if there were breakthrough pain, et cetera. In addition to that, bundling the medication is moving towards a less tailored approach as we, I think,

move towards an increased level of tailoring and treatments. And then lastly, the lack of clarity and confidence that I felt with regard to the risk mitigation strategies.

DR. CICCARONE: Dan Ciccarone. I voted no. It is difficult in this historically egregious opioid epidemic that we're experiencing to approve a new combination opioid drug; just hard, hard to look at the benefits outweighing the risk environment that we're in. I do applaud the attempts at risk mitigation using short-term dose restricted packaging, the return program. But since no data was presented showing that they would actually work in the real work, it remains a theoretical protective mechanism. So on the idea of preponderance of doubt, 51 to 49 percent, I voted no.

DR. KOTZ: This is Maggie Kotz, and I voted yes for several reasons. One, I guess I took a look at this as another opioid choice in terms of weighing risk versus benefit. I didn't feel like the risk was any greater than what it was being

compared to, the other hydrocodone-acetaminophen products on the market. I did share the concern about the abuse liability, however, again, just from the data and my clinical experience, I don't think the promethazine in this was going to make a big difference in its abuse liability.

I think that postmarketing is going to be extremely important. And as I mentioned, I don't think that the return program has any value at this point, but my understanding is this will be subject to the same REMS protocols that all the other opioids available are subject to.

In terms of the promethazine being compared to the other antiemetic ondansetron, I didn't have the data to compare how that's being used, how many doses are being used and whether it's being co-prescribed in a certain way, so I wasn't comparing promethazine to that.

The thing that allowed me to vote yes actually is the FDA's recommendation that the indications were changed to those who are prone to the OINV, and also that my understanding that when

this is prescribed, it won't be prescribed in the sense that you have to take everything that's in the package, but indeed that it will, from my understanding, be prescribed as you need it. So for me, there was more flexibility than I felt the discussion concluded.

DR. MICHNA: Ed Michna. I voted no, and I really wasn't concerned so much about the promethazine. It was the clinical reality of how this drug was going to be used. For this indication, I don't think they thought out this very well. To have a single dose with fixed dosing in the environment that we're in, it just doesn't make sense. That's just not the way we treat patients clinically.

If they wanted to go back and do some data on taking a half of tab or develop other doses that have some flexibility here, that makes more sense. But I think this drug, while a good idea, wasn't really well thought out in terms of how we use these drugs clinically.

DR. PORTER: Laura Porter. I voted no. I

didn't see any studies comparing pre-medication with antiemetics prior to opioids to this new drug, so in my opinion, it wasn't shown superior over the pre-medications. I also have a problem with new opioids being brought to the market with just slight changes in them. Also, I believe the benefits do not outweigh the risks of another opioid on the market.

DR. BATEMAN: Brian Bateman. I voted no. My concerns were around having patients incur the risks of high rates of drowsiness, confusion, syncope, and lower blood pressure, and potentially even respiratory depression associated with the addition of promethazine when it's being used in a prophylactic fashion such that many patients are potentially exposed to that medication unnecessarily. These side effects could be particularly problematic in older and frail patients and patients on concomitant medications as we discussed in the panel, which were underrepresented in the clinical studies.

I was also concerned about the medication

was only formulated at 7.5 milligrams of hydrocodone, which is higher than the typical starting dose of 5 milligrams. I think the dose-limited packaging is an important innovation and something that could potentially have real value. I note that the minimum package quantity was 18, and I think that number might be on the high side for what we would think of as the lowest possible dose for many indications like dental surgery, minor musculoskeletal injuries where maybe just 5 or 10 tablets would suffice.

I think the buyback program is also potentially a very valuable innovation, but I share the concerns of the rest of the panel that it was underdeveloped.

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

MS. ROBOTTI: Suzanne Robotti. I voted no, and I stated the reasons before. But I do want to point out that on the sponsor's slides, slide C-14, was the research statement, "Patients are willing to give up pain relief to avoid OINV." The U.S.

uses opioids much more than other countries. I don't see why we should be encouraging opioid use and making it easier to use. My primary problem with this drug combination is that combining the drugs offers no benefit from keeping then separate and could cause harm by overprescribing. The risks do not outweigh the benefit.

Just to clarify on the packaging issue, I'm not worried about the abusers. I'm worried about the misusers. I'm worried about those who have limited English skills or non-English literacy, so the visual packaging is very important. The words have to be very simple and very clear on the packaging because that's where misuse happens, and that's just not fair to anybody. Thanks.

DR. GALINKIN: Jeff Galinkin, and I voted no. When we think about promethazine, it was -- we did these studies. The FDA has requirements for bioequivalence, and that's how our PK was established for these in single-dose fashion. But promethazine was approved in 1951 before current federal regulations required multidose type

examinations.

We really don't use promethazine 6 times a day for 2 weeks at a time, and I'm concerned that they didn't do multidose PK or safety, particularly in at-risk populations such as obese patients or patients with sleep apnea. And they didn't look at patients who would be at risk also with the CYP2D6 metabolizers and whether that 5 to 10 percent of the population may have higher risks of side effects.

I also worry as a pediatric provider with this trickle down to kids. We in general in pediatrics have been moving away from fixed multidose products to single-dose products that are made specifically for each indication, and I personally prefer that type of regimen as opposed to doing multidrug combinations.

DR. MORRATO: Elaine Morrato. I also voted no, and like many have said, largely looking at it as a total benefit-risk balance. On one hand, I do agree, as we heard in the open public forum and from others, that nausea and vomiting is a serious

concern and consequence when you're thinking about pain management. I know it has consequences, but I was not sold on this as being a novel indication given that these are already existing marketed drugs and thereby necessitating what is the value of the combination versus the existing individual ones.

Overall, I found a real disconnect with the evidence that was presented versus potential real-world use: the dose, the pattern of combination, why isn't it currently being used, how is that information factored into the design of the drug development program. And as I mentioned earlier, I would encourage the sponsors. The buyback does sound conceptually great, but it is really lacking. I would really encourage you. Many states nationally, DEA, are emphasizing takeback programs. All right, maybe they're not paid, but there are a lot of lessons learned in just trying to do simple takeback programs twice a year in a local community, much less trying to return investment. So I would encourage you to

keep looking at it, but it needs a lot more work.

On another thing, just because this might have impact for other drugs FDA is evaluating in terms of the postmarketing REMS evaluation, I was happy to see that in the REMS standards now are 6-12-month intervals initially of looking at the impact. In the sponsor's book, I think they were going to do a physician survey, so I would encourage that. I'm assuming at 6 and 12 months, we're not just doing surveys but really doing some rigorous drug utilization analysis similar to what the FDA presented to us today.

DR. McCANN: Mary Ellen McCann. I voted no for the reasons that have been stated before.

DR. LITMAN: Ron Litman. I voted yes. As a middle-aged weekend warrior, I've had more than my fair share of operations, and I have been caught in this awful feeling between pain relief and nausea and vomiting, so I certainly can sympathize. On the other hand, I sit here as a government representative where I'm giving consultation to the FDA, whose job is to protect the American public,

and it's really a tough job to say when is something to risky to put out there.

But overall, from everything I've read about this and heard here today, I do believe that the very high-level benefit-risk ratio is favorable. I think that physicians like Dr. Lorenc, who testified here, are going to jump on the bandwagon and give this to their patients. And you know what? The patients are going to let them know within a very short time whether they're tolerating the increased anticholinergic effects like drowsiness, or delirium, or whatever there was.

I do want to say a few caveats, though. I completely agree with Jeff Galinkin's comments, and I would hope that the FDA would look at additional data for other populations such as older populations or those with the ultra fast metabolizers of CYPD26. I think in my question to the sponsor before, I was not convinced that we didn't see the toxicity when patients take more than 6 pills a day, and I would be very interested if I were the FDA in seeing that data to see what

kinds of side effects they had.

Finally, I'm not really sure how this enters into the FDA's decision of whether or not to approve, but I'm a little concerned that even if it's a minority of intravenous drug abusers who use this in its form, there will be -- so promethazine is a highly caustic irritant to skin tissues, and there is no doubt in my mind that when drug abusers use it for intravenous intention, they don't always get it intravenously. They could get it intra-arterially or just subcutaneously, and we will see people's hands or arms falling off if this happens.

I don't know how that is to be monitored or if that's a consideration. There's a famous case, Wyeth v. Levine that went to the Supreme Court, where a woman did lose her arm because it was administered intra-arterially by accident. So I think it's inevitable that if it's used recreationally with IV use, that this will happen, probably very occasionally. Anyway, overall I thought the benefits outweighed the risks.

DR. MEISEL: Steve Meisel. I voted no because I felt that the risks in this case outweighed the benefits. A number of points here. One is we're asking people to take a drug to prevent the side effect of another drug, but in itself is causing more side effects. And pretty soon we'll have another drug proposed to us that will mitigate the adverse effect of the second drug and so on. That's not the way to practice medicine or do business here. That's a very dangerous slope.

The fact that this is a single fixed-dose combination -- yes, I know a 5-milligram is in the works and a 10-milligram is in the works, this sort of thing, but we know that cisplatin causes an awful lot of nausea and vomiting, but we don't see it packaged with ondansetron. We give it separately in order to allow flexible dosing and all sorts of other things, and that's what needs to be the case here.

It didn't come up before. A point I want to make here is that when people get sick to their

stomach from an oral narcotic, it isn't for every dose for their duration of therapy. Oftentimes it's the first dose, the second dose, and then by dose 3, 4, 5, their body's adjusted and they may not need an antiemetic. They may not feel like they need something through that period of time. So that calls for PRN dosing of antiemetic prophylactically or therapeutically early on as needed, but that may not be needed for prolonged periods, whether it's 5 days, 6 days, 10 days, or 14 days. But if you use this drug, then you're going to get it for 14 days or whatever that time frame is, regardless.

So again, that flexibility just isn't there, and we're going to end up exposing people to medication that they otherwise don't need with all of the concomitant side effects.

I'm also unconvinced that there would be safety in the real world when it comes to drug interaction screening and drug interaction prevention, this sort of thing. There are an awful lot of people on drugs that will have additive and

maybe potentiating anticholinergic effects. Yes, you can build that into electronic health records as warnings, but those get overwritten, and we'll have all sorts of people in the real world with some serious anticholinergic effects because of the other medications they're on, and I'm not convinced that that's been well thought out.

Those are the reasons that I've got.

DR. CRAIG: Dave Craig. I voted no for many of the reasons the other committee members have already stated. I think in my opinion, it was the wrong choice of the antiemetic. I think that there's a reason why patients, who postoperatively get Zofran, for example, are on ondansetron as a choice versus other agents.

I teach a lot of lectures and things to students, and one of the things in one of my soapboxes is to avoid concomitant CNS depressants with opioids as much as possible. I think this is the opposite strategy.

I also have a lot of concerns about other trends, as Dr. Bateman had talked about with

Medicare, about looking at other opiate potentiators and the risks of using other CNS depressant drugs, and this could be one of them. I also have a lot of concerns about the fixed dosing schedule, which kind of flies in the face of individualized patient care. So those are some of my concerns.

DR. RAGHUNATHAN: Hi. This is Trivellore Raghunathan. This was a tough vote. I voted no. Mostly I can see the efficacy results, but I think that I was not convinced about the mitigation efforts and also the safety concerns that have been addressed.

Also, I think that the data that has been presented is such a limited population and the alternatives are not carefully evaluated, so it's kind of hard to judge, based on the data provided, whether or not this risk-benefit ratio offsets to vote in favor of this drug.

DR. SHOBEN: Abby Shoben. I also voted no. And I echo a couple comments that this actually was a very tough decision despite the seemingly

lopsided vote. For me, I was looking at the population level, considering the benefits to the population compared to the potential risks. And I think there is probably a slight risk as we discussed in question 3, a slight increase in risk over the comparison product, both in terms of potential abuse and misuse and in terms of the side effects to the individual patient.

So then the question is, does the benefit of prevention of this nausea and vomiting outweigh that? And to me, I didn't see evidence that this was a significant enough benefit to outweigh that increase in risk.

DR. WARHOLAK: This is Terri Warholak, and I voted no. One of the benefits of being on this side of the table is not many things haven't been said, so I voted no for many of the reasons that were noted before.

I think, in general, just the risk-benefit ratio compared to products that are already on the market and how they could be used in combination just didn't make sense to me, especially given the

potential unintended consequences on a population level.

DR. RUHA: Michelle Ruha. I voted no. Mainly, I really just don't favor adding in a drug to another drug that then gets dosed every time. I think that it has its own risk profile, and it also for many people isn't the preferred antiemetic. It would be to me a second line. I also think that it should be given as needed, and I agree that you may not need it with every dose of opioids. So those are the main reasons I voted no.

DR. CHOUDHRY: Niteesh Choudhry. I voted no for those same reasons.

DR. McCANN: Before we adjourn, are there any last comments from the FDA?

DR. HERTZ: I just want to thank everyone for their time. Some of you will be continuing on with us. We know that these committees have been requested to convene frequently, and we really appreciate the time taken from your busy schedules.

Adjournment

DR. McCANN: Thank you, panel members.

Please, for those of you especially who are leaving, take all your personal belongings with you. All material that's left on the table will be disposed of. We now adjourn this meeting. Thank you.

(Whereupon, at 12:26 p.m., the meeting was adjourned.)