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)

Virtual Meeting

Monday, November 2, 2020

9:00 a.m. to 1:09 p.m.

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. BATEMAN: Welcome. I'd first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Lauren-Jei McCarthy. Her email and phone number are currently displayed.

My name is Dr. Brian Bateman, and I'll be chairing this meeting. I will now call the November 2, 2020 joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order. Dr. Moon Hee Choi is the designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. CHOI: Good morning. My name is Moon Hee Choi, and I'm the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

Dr. Goudra?

(No response.)

DR. CHOI: Dr. Goudra, could you please unmute yourself if you are muted?

DR. GOUDRA: Yes, I'm unmuted. Basavana Goudra, anesthesiologist from Penn Medicine.

DR. CHOI: Dr. Higgins?

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

DR. CHOI: Dr. Horrow?

DR. HORROW: I'm Jay Horrow, clinical professor of anesthesia at the University of Pennsylvania where I attend to patients, and my main job is as clinical development lead in cardiovascular drug development at Bristol-Myers Squibb. I'm the industry representative to AADPAC.

DR. CHOI: Dr. Jowza?

DR. JOWZA: Hi. Good morning. My name is Maryam Jowza. I'm an assistant professor in anesthesiology and pain management at University of North Carolina.

DR. CHOI: Dr. McAuliffe?

DR. McAULIFFE: Good morning. I'm Maura McAuliffe. I'm professor of nursing and director of

the Nurse Anesthesia Program at East Carolina University, Greenville, North Carolina.

DR. CHOI: Dr. Shoben?

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

DR. CHOI: Dr. Sprintz?

DR. SPRINTZ: Hi. I'm Dr. Michael Sprintz, and I'm clinical assistant professor at University of Texas Health Science Center in Houston. I'm also CEO of Sprintz Center for Pain and Recovery just north of Houston. I'm boarded in pain medicine, addiction medicine, and anesthesiology, and I'm personally in recovery myself from addiction for over 20 years. Thank you.

DR. CHOI: Dr. Zaafran?

DR. ZAAFRAN: Good morning. Sherif Zaafran. I'm an anesthesiologist here in Houston, Texas. I'm with U.S. Anesthesia Partners, the largest anesthesia physician group in the country, and I'm also the president of the Texas Medical Board.

DR. CHOI: Dr. Zacharoff?

DR. ZACHAROFF: Hi. Good morning. I'm Kevin Zacharoff. I am faculty and clinical instructor and course director on pain and addiction at the Renaissance School of Medicine at Stony Brook University. My expertise is in anesthesiology and Pain Management. Thank you.

DR. CHOI: Dr. Calis?

(No response.)

DR. CHOI: Dr. Calis, are you muted by any chance?

(No response.)

DR. CHOI: Dr. Calis?

DR. CALIS: Yes, I'm sorry. This is Karim Calis. I am director of clinical research and compliance for the National Institute of Child Health and Human Development at NIH, and I'm also chair of the Intramural IRB. Thank you.

DR. CHOI: Dr. Habel?

DR. HABEL: Yes. Good morning. This is Laurel Habel. I'm an epidemiologist and the associate director at the Division of Research at Kaiser Permanente, Northern California.

DR. CHOI: Dr. Hernandez-Diaz?

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

DR. CHOI: Dr. Hovinga?

DR. HOVINGA: Collin Hovinga. I'm a clinical pharmacologist and epidemiologist, a faculty appointment at UT Austin, and I'm also the senior vice president for clinical and scientific development at I-ACT for Children.

DR. CHOI: Dr. Mehta?

DR. MEHTA: Hi. Reema Mehta, head of Risk Management and Safety Surveillance Research at Pfizer, serving as the nonvoting industry rep.

DR. CHOI: Dr. Meisel?

DR. MEISEL: Good morning. Steve Meisel. I am a director of medication safety for M Health Fairview integrated health system based in Minneapolis.

DR. CHOI: Dr. Nelson?

DR. NELSON: Good morning. I'm Lewis Nelson. I'm professor and chair of emergency medicine and a medical toxicologist at Rutgers New Jersey Medical

School in Newark, New Jersey, and I'm a senior consultant to the New Jersey Poison Center.

DR. CHOI: Dr. Soko Setoguchi let us know about a last-minute personal matter and won't be attending today.

Dr. Arfken?

DR. ARFKEN: Good morning. This is Cynthia Arfken. I'm an epidemiologist and professor in psychiatry at Wayne State University in Detroit, Michigan.

DR. CHOI: Dr. Bateman?

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

DR. CHOI: Dr. Ciccarone?

DR. CICCARONE: Good morning. This is Dan Ciccarone. I am professor of Family and Community Medicine at University of California, San Francisco, and I'm board certified in family medicine and addiction medicine.

DR. CHOI: Dr. Hincapie-Castillo?

DR. HINCAPIE-CASTILLO: Good morning. Juan

Hincapie-Castillo. I am an assistant professor of pharmaceutical outcomes and policy at the University of Florida College of Pharmacy.

DR. CHOI: Dr. McCann?

DR. McCANN: Hi. Good morning. I'm an associate professor of anesthesiology at Harvard Medical School and a pediatric anesthesiologist at Children's Hospital in Boston.

DR. CHOI: Dr. Michna?

DR. MICHNA: Hi. Ed Michna, anesthesiologist, pain management, Brigham and Women's Hospital in Boston.

DR. CHOI: Dr. Porter?

DR. PORTER: I am the medical affairs senior consultant and patient advocate with the Colorectal Cancer Alliance and a stage 4 colon cancer survivor.

DR. CHOI: Dr. Thanh Hai?

DR. THANH HAI: Good morning. This is Mary Thanh Hai. I'm the acting deputy director in the Office of New Drugs.

DR. CHOI: Dr. Roca?

DR. ROCA: Good morning. This is Rigo Roca.

I am the division director for the Division of Anesthesiology, Addiction Medicine, and Pain Medicine in the Office of Neuroscience.

DR. CHOI: Dr. Staffa?

DR. STAFFA: Good morning. This is Judy Staffa. I'm the associate director for Public Health Initiatives in the Office of Surveillance and Epidemiology, in CDER at FDA.

DR. CHOI: Dr. LaCivita?

DR. LaCIVITA: Good morning. My name is Cynthia LaCivita. I'm the director for the Division of Risk Management in the Office of Surveillance and Epidemiology in CDER at FDA.

DR. CHOI: Thank you.

DR. BATEMAN: For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this 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 productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open form of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Dr. Moon Hee Choi will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration, FDA, is convening today's joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members and temporary

voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of these committees' compliance with the federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

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

the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, C-R-A-D-As; 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 Olas Pharma, Incorporated, that has hydrocodone, acetaminophen, and promethazine, for the short-term, not to exceed 3 days, management of acute postoperative pain severe enough to require an opioid analgesic and the prevention of opioid-induced nausea and vomiting in patients who are at risk for or have a history of nausea and vomiting.

This is a particular matters meeting during which specific matters related to Olas Pharma's NDA will be discussed. Based on the agenda for today's meeting and all financial interest 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 have been made concerning the product at issue.

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

We would like to remind members and temporary voting members that if the discussions involve any

other product or firm not already listed in the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committees of any financial relationships that they may have with the firm at issue. Thank you.

DR. BATEMAN: We will proceed with the FDA's opening remarks from Dr. Rigoberto Roca, the director of the Division of Anesthesiology, Addiction Medicine, and Pain medicine.

FDA Opening Remarks - Rigoberto Roca

DR. ROCA: Good morning, Dr. Bateman, members of the AADPAC and DSaRM committees, and invited guests. This is Rigo Roca, and as was just noted, I am the division director of the review division that is responsible for this particular product, the review of this product.

This morning we will be discussing the application by Olas Pharmaceuticals for Hydexor, which is a combination product containing hydrocodone,

acetaminophen, and promethazine. As many of you are aware, the application for this product was brought before these committees on February 14th of 2018. The purpose of today's meeting is to discuss whether the currently proposed indication and the REMS have adequately addressed the concerns identified during that advisory committee meeting.

In the next few minutes I would like to briefly review the agenda for today's meeting. After the applicant's presentation, Dr. Tieu and I will present the FDA perspective. That will be followed by a break and the open public hearing. After the open public hearing, I will give the charge to the committee. We look forward to your discussions, and we thank you for taking the time away from your busy schedules to assist us.

Dr. Bateman?

DR. BATEMAN: Thank you.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA

believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including Olas Pharma's non-employee presenters, to advise the committee of any financial relationship that they may have with the sponsor such as consulting fees, travel expenses, honoraria, and interest in the 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 relationship. 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 Olas Pharma's presentations.

Applicant Presentation - George Scott, Jr.

MR. SCOTT: Thank you.

Good morning. My name is George Scott, and I'm the executive VP of corporate affairs for Olas Pharma, Incorporated, the sponsor of Hydexor. I also

serve as the company's chief legal officer. To clarify, Olas Pharma is the wholly-owned subsidiary of Charleston Laboratories.

We are here today to discuss with you our full agreement and alignment that Olas Pharma has reached with the agency in regards to addressing the concerns raised by Hydexor's first advisory committee meeting on February 14, 2018, which will enable Hydexor, a novel medication with a novel indication, to be available to a limited medically-supervised patient population, which is subject to its own product-specific comprehensive REMS to prevent opioid-induced nausea and vomiting, or OINV, in order to address the unmet need of postoperative patients at high risk of OINV with hydrocodone-containing products.

No matter how you become nauseous, it is a feeling no one desires. Whether it comes from morning sickness, a migraine, seasickness, terrible food poisoning, or chemotherapy, suffering nausea is suffering nausea. No matter how it is caused, you will do almost anything to avoid it.

When someone already has an underlying painful

condition, adding nausea to such suffering only magnifies the patient's agony physically and emotionally. Ironically, it is an ailment that is so common as a side effect, we often minimize impact on patient; that is until you or someone you care for suffers from it.

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 the healthcare system through suboptimal patient recovery, poor patient outcomes, including inadequate pain management, and increased costs. OINV is the primary reason for non-adherence or discontinuation of IR opioids, and once it occurs, OINV is difficult to control.

Patient reports of nausea and the severity are regularly cited as important side effects by drug regulators. In 2018, the FDA congregated an advisory committee meeting which addressed the importance of nausea as a significant adverse effect of opioids. There are many drugs at which the incidence and

severity of nausea have played a prominent role in the drug label and use, even rejection of the proposed drugs.

Currently, there are no medications approved to specifically and proactively manage OINV. Hydexor will be the first and only product with clinical data supporting the management of OINV. Physicians may have other options to treat OINV, but none are so indicated or have clinical data to understand the associated risk. We come before you today reaffirming our commitment to responsibly bring this novel medication to a specific and narrow patient population and certified medically-supervised settings, thus responsibly improving patient options for their acute postoperative pain management.

Hydexor is a unique formulation using well-characterized, approved analgesic and antiemetic compounds supported by a robust clinical development program, uncommon among 505(b)(2) applications. Hydexor contains immediate-release hydrocodone and acetaminophen, along with a novel formulation of promethazine. We selected the lowest oral solid dose

of promethazine, which is half to one-quarter of what is typically prescribed for nausea and vomiting.

As you know, the agency has agreed that Hydexor met the requirements for approval under the 505(b)(2) regulatory pathway. This NDA is supported by a comprehensive development program. Hydexor demonstrated bioequivalence to its RLDs and Norco, the active comparator. In addition, efficacy was shown in two phase 3 clinical trials that met the co-primary and key secondary endpoints.

The safety of Hydexor was established in the analysis of over 642 patients exposed to Hydexor throughout the two pivotal trials and one actual-use safety study. Throughout the clinical program, no new safety signals were identified. Olas has completed a human abuse liability study that showed no increase in the abuse potential of Hydexor compared to Norco at supratherapeutic doses.

This development program demonstrated Hydexor's efficacy in the short-term management of acute pain and prevention of opioid-induced nausea and vomiting and established a safety profile consistent

with its individual components.

Today's brief agenda is reflective of our appreciation for you having read the Olas Pharma and FDA briefing document that provide the regulatory history and previous AdCom concerns. While the February 2018 AdCom included the public testimony of several independent experts from the sponsor, today we will focus on the agreement we have reached with the FDA to address the concerns outlined by the February 2018 AdCom to revise the labeling and develop a REMS program unique to Hydexor to include significant limitations in patient population, duration, dose, and setting.

Dr. Bernard Schachtel will discuss the clinical efficacy and safety attributes of Hydexor through the lens of the revised labeling and comprehensive product-specific REMS program. I will return to further discuss the changes to our labeling and the addition of a product-specific REMS program unique to Hydexor, and describe the patient journey, which emphasizes our willingness to engage with the FDA to address the concerns identified at the February 2018

AdCom.

We are also fortunate to have as a respondent our president and CEO, Paul Bossee, as well as an internationally renowned authority on nausea and vomiting in the postoperative setting, Dr. TJ Gan, from the Renaissance School of Medicine at Stony Brook University, as an additional expert to help answer questions posed by today's committee.

I now will have Dr. Schachtel more specifically discuss our clinical efficacy and safety with respect to our modified labeling.

Dr. Schachtel?

Applicant Presentation - Bernard Schachtel

DR. SCHACHTEL: Thank you, George.

Members of the advisory committees, it's my pleasure to speak with you today. You've received the briefing documents prepared by FDA and Olas Pharma, and with these as background information, I would like to discuss the salient features of the findings of the phase 3 trials in the Hydexor application, showing the relevance to the label and the REMS program. These were developed in response to the 2018 advisory

committees' concern about the possible adverse event of sedation for patients who may be prescribed Hydexor, but who may not be at risk of developing OINV.

As Dr. Roca said, it is because of the advisory committees' input that we are here today to discuss the FDA and Olas Pharma agreed label and product-specific REMS for Hydexor. Throughout, you will notice agreement between FDA and Olas Pharma regarding the findings of the phase 3 studies that led to the label and REMS you are reviewing today.

I intend to relate the label and REMS program to three conclusions: showing that the new indication addresses the 2018 advisory committees' advice to identify patients appropriate for treatment with Hydexor, that is patients at high risk of developing OINV; showing that patient-reported nausea is important, as nausea is a symptom which physicians inquire directly about in order to identify this target population; and showing that the components of the label and the Hydexor-specific REMS mitigate potential adverse events that may occur in postoperative patients who receive Hydexor in an inpatient setting.

From the beginning of the clinical development program, the efficacy standard for approval of Hydexor was jointly agreed. The pivotal phase 3 studies were required to demonstrate that Hydexor is effective as an analgesic compared to placebo and that Hydexor is effective compared to hydrocodone/acetaminophen, Norco, in reducing the incidence of nausea and vomiting, that is in preventing OINV.

The two pivotal trials were multicentered, randomized, double-blind, active, and placebo controlled. Study 002 was an oral surgery acute pain model and Study 003 was a post-bunionectomy acute pain model. As you can see, pain reduction was demonstrated over the first 24 hours in the 002 study. The 003 study demonstrated the analgesic efficacy of Hydexor over a 48-hour treatment observation period.

OINV was defined as the occurrence of vomiting and/or use of antiemetic medication, over 24 hours in the 002 study and over 48 hours in the 003 study. This 2-component OINV endpoint was met in both studies, showing clinically significant relative risk reduction.

It is important to note that in the 003

post-bunionectomy study, patients were evaluated and monitored over 48 hours as inpatients, similar to how postoperative patients will be administered Hydexor in the proposed label, in an medically-supervised environment while being monitored carefully during their inpatient stay.

The co-primary outcomes in the 002 study were substantiated by prespecified key secondary and other secondary endpoints. Noteworthy is that all key secondary OINV endpoints in the 002 study supported the conclusion of OINV prevention, including the finding that compared to Norco, Hydexor reduced the intensity of nausea as well as the frequency of vomiting over the first 24 hours, which was the treatment observation period of that study.

This reduction in nausea intensity observed in the 002 study was confirmed over 48 hours in the 003 study, where the intensity of nausea was significantly reduced for Hydexor-treated patients compared to Norco-treated patients. I bring this up to underscore the clinical importance of nausea to the assessment of OINV.

Patient ratings on the Nausea Intensity Scale, or the NIS, a standard 0 to 10 Likert scale, add to our recognition and appreciation of the extent of OINV in the controlled trials. Because of the relevance of opioid-induced nausea to the detection of OINV, in fact a 3-component OINV endpoint was also analyzed in both trials. It included the occurrence of any moderate or severe nausea without any vomiting --

DR. CHOI: Dr. --

DR. SCHACHTEL: Yes?

DR. CHOI: I'm sorry. Dr. Schachtel?

DR. SCHACHTEL: Yes?

DR. CHOI: We are not able to see your slides. Can we take a quick break?

DR. SCHACHTEL: Of course.

(Pause.)

DR. BATEMAN: We're still working through the issues around the presentation. We'll give you an update as soon as we know anything.

(Pause.)

DR. SCHACHTEL: Hello? This is Bernie Schachtel again. Can you hear me now?

DR. BATEMAN: We can.

DR. SCHACHTEL: Oh, great.

Dr. Bateman, you'll appreciate this. I believe when I was an academic consultant and presenting to the advisory committee in the 1990s, a light bulb went out on the slide projector during an advisory committee meeting, and I had to proceed without any slides. So this is an improvement for sure. I appreciate it.

DR. BATEMAN: Bernie, please start with CC-4.

DR. SCHACHTEL: I think that where I'd like to start is actually on CC-7, please. CC-7 is supposed to show what I was talking about in terms of -- there it is. Okay. We're on the same page now.

What I was saying here is that the finding among the secondary endpoints that supported the conclusion of OINV prevention was showing that Hydexor reduced the intensity of nausea over the initial 24-hour treatment observation period in the O02 study. If you look at that slide and see the results for over 24 hours in the first controlled trial, you'll see that this reduction of nausea intensity was confirmed over

48 hours in the 003 study.

Here you can see that the intensity of nausea was significantly reduced for Hydexor-treated patients compared to Norco-treated patients. I think you can also observe that between 24 and 48 hours -- if you can sort of project -- the nausea severity actually worsened in the Norco group and actually improved in the Hydexor group.

But I bring this up, really, to underscore the clinical importance of nausea to the assessment of OINV. Patient ratings on the Nausea Intensity Scale, or NIS, which is a standard 0 to 10 Likert scale, add to our recognition and appreciation of the extent of OINV in the controlled trials.

Because of the relevance of opioid-induced nausea to the detection of OINV impact, a 3-component OINV endpoint was also analyzed in both trials. It included the occurrence of any moderate or severe nausea with any vomiting or use of antiemetic as evidence of OINV, and this 3-component OINV endpoint provided supportive evidence of preventative antiemetic activity by Hydexor in both studies.

It is in this context that FDA's analyses of patient assessments on the Nausea Intensity Scale in the 003 study are particularly insightful I believe. This figure shows the relationship between the severity of nausea, patients' ratings from 0 to 10 on the NIS on the X-axis, and the subsequent use of rescue antiemetics. A greater proportion of patients with NIS scores greater than 3, that is patients with more than mild nausea, tended to request antiemetics later. Twenty-five percent of patients with an NIS score of 6, for example, subsequently used an antiemetic.

This research may have identified a clinical useful relationship. Patient-reported NIS scores increasing towards and then greater than 3 appear to represent relatively more severe nausea and may be indicative of a patient's worsening clinical status. One example of worst clinical status in the postoperative setting of course is retching. For this reason, we measured episodes of retching as well as episodes of vomiting in the O03 study.

As observed over the initial 48 hours of opioid treatment, we learned there was 63 percent

relative reduction in the risk of developing emetic episodes for patients using Hydexor compared to patients using Norco. Patient reports of nausea are critical signals to practitioners who care for postoperative patients. They know firsthand that nausea can be a very annoying or even agonizing symptom for some patients, and then nausea may be the harbinger of worst clinical conditions such as retching, vomiting, aspiration, and surgical complications. Clinicians know that preventing postoperative nausea can improve pain management.

FDA's review of the OINV data from the 003 study and the 3-day duration of use proposed for the Hydexor label led us to present the OINV outcomes over 3 days. Note for example the incidence of nausea and of moderate to severe nausea among patients using Norco over 3 days. As you can see, 83.2 percent of Norco-treated patients experienced opioid-induced nausea with 51.6 percent reporting moderate to severe nausea. Over 3 days, 24.4 percent of Norco-treated patients vomited at least once; 28.8 percent had been retching at least once.

Now as you can see in the bottom of this slide, for Hydexor-treated patients, the frequencies of these OINV outcomes differed noticeably and significantly from Norco-treated patients. Looking at the 3-component endpoint in the far-right column, for example, which includes moderate to severe nausea as a component, you can see that compared to patients using Norco, significantly more patients using Hydexor had no vomiting, no use of rescue antiemetic, and only mild or no nausea.

The frequency of nausea, especially moderate to severe nausea, was lower among patients taking the same number of doses of Hydexor over 3 days. This reduction in the occurrence and severity of nausea further informs the therapeutic benefit of Hydexor. Especially as suggested by the research from FDA above, more severe nausea is indicative of a patient's worsening clinical status for there were also notable differences observed over 3 days in the frequencies of vomiting and retching, indicating fewer emetic episodes among Hydexor-treated patients.

Nausea is consequential to postoperative

patients as well as to the physicians attending them. When they interview their patients, reviewing their medical records and inquiring about risk factors for postoperative nausea and vomiting, clinicians identify patients at high risk for OINV. As a result of their identification of these patients, we anticipate that the opioid-induced nausea and other emetic outcomes observed in these studies can accordingly be prevented in practice.

Now I would like to add some comments on the other safety data presented in the briefing documents, showing how the label and product-specific REMS will mitigate adverse events that may occur.

FDA provided a definitive plan for the evaluation of the safety of Hydexor. Based on considerable knowledge about the therapeutic use of immediate-release hydrocodone/acetaminophen and many years knowledge about promethazine, in particular when used in higher dosages, the FDA directed that there would be no need for a phase 2 dose-finding study. FDA approved testing the 7.5-milligram dose of hydrocodone and the 325-milligram dose of acetaminophen, combined

with the lowest approved dose of promethazine, 12.5 milligrams, and Olas Pharma was advised to proceed directly to phase 3 evaluation.

To provide an ample safety database on the use of Hydexor, in addition to the 002 and 003 studies, FDA requested a third phase 3 study, a multicentered, open-label, safety in-use study, 006. This safety study was conducted on 179 patients with an acute flare osteoarthritis of the knee or hip inadequately treated with an NSAID. The intent of this actual-use study was to document adverse events under real-world conditions. It was conducted to examine the safety of Hydexor when used as needed without medical supervision rather than on a fixed schedule regimen as in the 003 study.

Because of its extensive safety database on therapeutic uses of hydrocodone, acetaminophen, and promethazine, FDA advised that the safety database for Hydexor should comprise approximately 600 patients using Hydexor in clinical settings. In the safety evaluations of Hydexor in the 002, 003, and 006 studies, there were 642 patients treated with repeated doses of Hydexor.

Except nausea and vomiting adverse events which were documented as OINV efficacy endpoints, other adverse events were assessed in two ways in the two controlled trials, by assessments of 9 common opioid-related side effects on 11-point Likert scales and by standard patient reporting of any other adverse events.

A comprehensive analysis of safety was reviewed at the first advisory committee meeting and in the briefing documents. Therefore, just as I summarized the efficacy findings over 3 days as they relate to the label and REMS that we are discussing today, I would now like to summarize the safety observations from the controlled clinical trials over 3 days.

The adverse event of most concern to the 2018 advisory committees was sedation, which was the most common adverse event for all patients in the controlled trials regardless of treatment. 91.7 percent of Hydexor-treated patients reported drowsiness over 3 days, an incidence that was higher than the 85.6 incidence among Norco-treated patients and

54 percent of placebo-treated patients, indicating a high background rate.

As assessed on the 0 to 10 drowsiness scale, the mean severity of drowsiness in the Hydexor-treated group was 3.91, greater than the 2.58 mean severity recorded by Norco-treated patients or placebo, which was 1.28. Patients taking Hydexor reported more severe drowsiness than Norco- or placebo-treated patients.

It is worth noting in this context that when patients used Hydexor as needed in the 006 actual-use study, 18 percent of them reported drowsiness, and as in the controlled trials, none had serious medical consequences related to Hydexor. This evidence of safe use of Hydexor on conditions of actual use adds another perspective to the safety assessment of Hydexor. It is also relevant to the evaluation of the proposed label and REMS, which will mitigate any adverse events of excessive sedation that may occur when patients use Hydexor as needed under close medical supervision.

Overall, Hydexor was well tolerated in the clinical trial. Most of the adverse events were in the mild or low-moderate range of severity with ratings of

4 or lower on the 11-point opioid symptom scale, and they were of limited duration. No adverse event caused any interruption of study drug utilization and no adverse event resulted in a patient's discontinuing his or her use of study medication.

There were no clinically significant drug related sequelae such as a fall, even among patients who reported severe drowsiness, which was reduced in incidence and severity as dosing decreased, and all adverse events resolved without recurrence as patients continued using study medication. There were three serious adverse events among all patients in controlled clinical trials, none drug-related, and no respiratory depression. There is no evidence of increased risk of respiratory depression with Hydexor compared to Norco.

Finally, there were no new safety signals. As a result, for clinicians there is a predictable and manageable safety profile for Hydexor which utilizes the lowest approved 12.5-milligram dose of promethazine, lower than 25- and 50-milligram oral doses customarily prescribed for adults, resulting in considerably lower total daily dose of promethazine.

While no serious adverse events occurred during the 48-hour treatment observation period of Study 003, it is worth noting again that patients were required to stay in the study for the first 48 hours of this study and were subject to careful observation. These inpatient conditions of careful observation are proposed among the safeguards, which the label stipulates for the use of Hydexor. With this in mind, I would like to summarize how the proposed Hydexor label and REMS respond to the advice from FDA and the 2018 advisory committees.

First, the drug is to be administered only to postoperative adult patients who are at high risk of nausea and vomiting from hydrocodone-containing products. Physicians in practice know their patients, and they know how to identify high-risk patients. These patients will comprise the targeted populations for the prescription of Hydexor.

To assure monitoring and management of potential side effects, including fall prevention protocols, which are already operational for post-op patients in the hospital, Hydexor will be available

only for inpatient use in certified, medically-supervised healthcare settings such as hospitals and surgical centers.

Administration of Hydexor will be limited to 3 days in the inpatient setting, and the proposed label limits use of Hydexor to 5 tablets per day. This reduced total daily dosage should further enhance the safe and effective use of Hydexor, as should the limitation to a maximum of 15 tablets that may be dispensed for a patient. Hydexor should be used only when non-sedating alternatives are either not tolerated or not effective.

Finally, a REMS program specific for Hydexor and meeting FDA standards will be operational for all facilities where Hydexor is dispensed. This REMS program was designed to assure that only certified wholesalers distribute Hydexor to certified healthcare settings where personnel are trained to administer Hydexor and to manage side effects if they occur.

In conclusion, I hope that this review of the findings from the phase 3 studies helps you understand the clinical benefits of Hydexor for post-op patients

and how the targeted label and REMS program will mitigate any potential adverse event. Together this label and REMS program will enable the safe use of Hydexor by post-op patients at high risk of OINV, providing good pain management.

Now I'll turn the virtual podium back to George.

Applicant Presentation - George Scott

MR. SCOTT: Thank you, Dr. Schachtel.

I would now like to discuss the evolution of Hydexor's label and how Hydexor's current label addresses the concerns of the previous AdCom. At the time of the February 2018 AdCom, Hydexor's proposed indication was for the short-term, generally less than 14 days management of acute pain, severe enough to require an opioid analgesic while preventing opioid-induced nausea and vomiting in patients expected to be prone to nausea and vomiting. Hydexor was being proposed for both the inpatient and the outpatient, regardless of OINV risk status.

Hydexor's clinical program was the genesis of this original indication, as it consisted of studies

traditionally accepted as model for treatment of general acute pain that were enriched with a population likely to experience OINV, and included safety data for 14 days of treatment. The agency agreed that Hydexor was efficacious with respect to pain and OINV. The agency also concluded that Hydexor did not pose any serious adverse events of consequence and was safe in the proposed patient population.

As a result of the 2018 AdCom, the agency did not approve Hydexor, stating that Olas did not identify a patient population that predictably requires concomitant therapy with an opioid analgesic and a pre-emptive antiemetic. To clarify, although the agency's complete response letter seemed to suggest that Hydexor's clinical trials needed to demonstrate effectiveness with every dose for every patient, the agency clarified that this was not the standard of approval and not required to meet the combination.

The agency's concern was that the antiemetic component of Hydexor was not needed by a majority of patients in the two pivotal studies, however, the agency again clarified that there was no regulatory

requirement that a majority of patients have this need. This concern was based on analysis using the conventional regulatory 2-component definition of patients treated with Norco and Hydexor's 003 clinical trial, and it concluded that since the majority of patients treated with Norco did not experience OINV, the majority of patients being prescribed Hydexor in practice could be exposed to the potential risk of promethazine without receiving its benefit.

The agency's analysis was limited to the standard regulatory definition of opioid-induced nausea and vomiting, which consists of two objective criteria, vomiting and/or requesting an antiemetic. However, as physicians appreciate and the agency has agreed, patient-reported nausea can merit treatment with an antiemetic.

A 3-component definition of OINV, including any moderate to severe nausea, vomiting, or use of an antiemetic, is indicative to how physicians understand and detect nausea and vomiting in practice and is more reflective of how patients report nausea and vomiting. The literature of OINV reflects patient-reported

nausea, which reports approximately 40 percent of patients exposed to an opioid in the postoperative setting experience nausea, and it's not limited to nausea for which patients request an antiemetic.

When patient-reported nausea is taken into account, the analysis of patients treated with Norco in the 003 Hydexor clinical trial for days 1 through 3 shows that the majority, over 83 percent, of patients did experience opioid-induced nausea. Almost 52 percent of Norco-treated patients reported moderate to severe nausea, which the agency has acknowledged may require an antiemetic. Thus, when considering the 3-component definition of OINV in days 1 to 3 post-surgery, a majority, 56 percent, of Norco-treated patients experienced OINV, which may require treatment with an antiemetic.

In her judgment, as noted in the FDA briefing document, Dr. Thanh Hai, now acting deputy director for the Office of New Drugs, acknowledged the importance of patient-reported nausea as she stated that, "Efficacy was established with both the 2-component and 3-component endpoints. There is validity in accepting

the analyses based on the NIS" -- that is the Nausea Intensity Scale or patient-reported nausea -- "as supportive evidence that a significant proportion of patients experienced symptoms that could merit treatment with an antiemetic."

Understanding the concern that not all nausea may warrant the use of an antiemetic, all nausea does impact patient recovery, especially in the postoperative setting. The 2018 AdCom concern regarding giving an antiemetic to a patient with nausea, but potentially not severe enough to utilize an antiemetic, is a legitimate theoretical concern.

Based on the clinical data, the most likely additional risk of the use of Hydexor and the patient at risk for or experiencing nausea is an increased risk of severe drowsiness. However, the modification to the Hydexor label and REMS more than adequately mitigate this concern by its restriction to a monitored setting in a patient population more likely to experience OINV and where OINV can have the greatest impact on patient recovery.

Thus, with the agency's acknowledgement of the

significance of patient-reported nausea and clarification of the standard of regulatory approval, we worked with the agency to reach agreement on the appropriate label that clearly identifies the patient population that would most benefit from Hydexor and mitigate risk to patients through labeling and REMS.

Let's take a more detailed look at this new indication and Hydexor REMS and the previous AdCom's concerns. The previous AdCom concerns fell into three major categories: commercial or clinical practice concerns; concerns regarding exposing patients to sedative risk of promethazine who may not need its benefit; and those related to the mitigation of abuse or misuse. The agency and Olas agree that the new proposed label and REMS adequately address all such relevant concerns.

With respect to commercial concerns, although we are not here to address those concerns, nor are they relevant to the standard for approval, the worries such as packaging, CYP-2D6, and physician targets are now addressed by Hydexor's new label and REMS.

With respect to concerns regarding exposing

patients not at risk for OINV to the potential sedative risk of promethazine, which was the concern that drove the agency to issue a complete response letter, let's look at how the new indication and Hydexor REMS address this concern.

Hydexor's clinical data showed no serious adverse events of consequence, including zero cases of falls or respiratory depression. These data include an actual-use safety study for 14 days where patients were allowed to continue their normal daily activities and 39 patients taking supratherapeutic doses of 5 times the prescribed dose. That's in our human abuse liability study.

There were more instances of severe drowsiness, which although there were no consequences seen in our clinical trials in such instances, the risk of drowsiness is something that we've mitigated through labeling and REMS, which include specific safety protocols and procedures for postoperative inpatients. Nonetheless [indiscernible], Hydexor's current proposed indication limits promethazine exposure to 3 days in post-surgical inpatients at high risk of OINV, patients

who are most likely to receive the greatest benefit of prevention of OINV.

Further, Hydexor will be administered only by healthcare professionals certified as trained to administer Hydexor. Thus, if any serious side effects of consequence do occur, which did not occur in our trials, they will transpire while the patient is being monitored by certified healthcare professionals trained to deal with the risk of Hydexor, including a fall protocol, which is part of Hydexor's REMS.

With respect to concerns related to abuse or misuse, there was no difference shown in abuse potential versus Norco, nor any instances of respiratory depression. Hydexor is now limited to postoperative inpatient in certified healthcare settings. It will not be available at retail pharmacies.

Thus, Hydexor will only be distributed from the manufacturer to certified wholesalers who certify that they will only distribute Hydexor to these certified healthcare facilities, which will have healthcare professionals trained to administer Hydexor

and manage any of its side effects, and also trained not to dispense Hydexor outside of such medically supervised settings.

Patients will receive 1 Hydexor tablet at a specified time and measured only by a certified healthcare professional on an as-needed basis in a supervised medical setting. Thus, any risk of misuse or abuse that's adequately mitigated, such mitigation is governed by Hydexor's comprehensive REMS program unique to Hydexor.

To provide context of this discussion, I now want to outline what a Hydexor patient journey would entail pursuant to its label and product-specific REMS. The Hydexor patient journey, with respect to its agreed label and its REMS program, is direct, closely monitored, limited in duration, and only applicable to surgical inpatients.

The journey begins in the pre-surgery period where the patient undergoes comprehensive tests and a review of their medical history to ensure they are fit for surgery and to identify any risk factors. This period is usually 2 to 4 weeks, but varies depending on

the type and urgency of the surgical procedure.

On the day of surgery, the patient is admitted to the hospital and given a patient-specific barcode bracelet used for the patient identification throughout the remainder of their stay. Prior to surgery, the patient's identification, medical history, and any potential risks are confirmed. The patient then receives an IV and is connected to the vital-sign monitor.

The surgery is performed and the patient is transferred to their inpatient stay room where the patient's care is closely monitored on a schedule that includes blood work, vital signs, wound healing, and pain management. Provided the healthcare facility is certified through the Hydexor REMS program, it is in this immediate postoperative period that the patient may be prescribed Hydexor.

To administer Hydexor, the medical professional must obtain the tablet from the hospital pharmacy pursuant to standard operating procedures which monitors all scheduled medication. The medical professional scans the barcode of the patient to ensure

the correct patient is receiving this medication and to prevent medication errors or potential drug-drug interaction. The patient must ingest the tablet in the presence of the medical professional.

The patient is connected to a vital-sign monitor during this inpatient period with scheduled workups ensuring any potential risks will be constantly monitored, providing additional protection for patients receiving Hydexor.

The maximum number of Hydexor tablets that the patient could receive is 15, 5 per 24-hour period over 3 days. If the patient remains in the hospital longer than 3 days and still requires an opioid medication for pain control, they would need to be transitioned to an alternative medication, as Hydexor will only be available in certified healthcare facilities for postoperative inpatients which have fall protocols on site. It will not be available to physicians or patients in the post-discharge outpatient retail setting. This means that upon discharge, patients will not have access to Hydexor from their doctors or at their local retail pharmacy.

The revised labeling and Hydexor REMS made the Hydexor patient's journey direct, supervised, and safe. Hydexor is a safe and effective solution for patients who need pain management and are at high risk of opioid-induced nausea and vomiting from hydrocodone products.

As we discussed, the original indication had the intended population as all acute pain patients expected to be prone to nausea and vomiting for up to 14 days and no more than 6 pills per day, with pain severe enough to require an opioid when non-opioid alternatives are either not tolerated or ineffective. Let's explore the differences between the original label and the new label you see before you.

Hydexor is now indicated for the management of acute postoperative pain severe enough to require an opioid analgesic, not all acute pain patients. Hydexor can only be used in postoperative adults at high risk for nausea and vomiting with hydrocodone-containing products, a significantly smaller subset of adults expected to be prone to nausea from any opioid product.

Previously, Hydexor was proposed when any

alternative therapy was not tolerated or effective. That has been further restricted to any non-sedating alternative therapy. Hydexor is now limited to 3 days or less of therapy, with no more than 5 pills per day, versus the prior proposal of 14 days or less and no more than 6 pills per day.

Further, Hydexor has limited use in certified, medically-supervised healthcare settings such as hospitals and surgical centers. In addition, Hydexor is subject to a unique product-specific comprehensive REMS more regimented than standard classwide REMS, which ensures that only certified wholesalers distribute Hydexor to certified healthcare settings, which have on-site fall protocols with personnel trained to administer Hydexor and manage its side effects.

We are proud to say that with respect to Hydexor, the advisory committee process works. After considering the committee's concerns raised in 2018, we've worked with the agency and have reached agreement and full alignment on how to move forward with Hydexor, with a revised label in postoperative inpatients at

high risk for OINV from hydrocodone-containing products, in a certified, medically-supervised setting for a limited duration.

Also, unlike other immediate-release opioids like Norco and other IR hydrocodone products in the inpatient setting that do not have a REMS program, Hydexor is subject to its own comprehensive REMS, which ensures, among other things, that Hydexor is only distributed in the inpatient setting by certified healthcare professionals.

In summary, OINV creates a significant burden in the postoperative inpatient setting. Hydexor has demonstrated efficacy in the postoperative inpatient setting, both in terms of pain relief and sustained prevention of OINV for the 3-day inpatient period. Throughout the clinical program, no new safety concerns were identified, for the expected increase in the incidence in the intensity of drowsiness is now mitigated to the revised label and REMS program, which is unique to Hydexor.

These attributes, coupled with Olas Pharma's commitment to responsible use, create a favorable

benefit-risk profile for Hydexor. Thank you for your time this morning, and thank you for bearing with us through our technical difficulties. We look forward to addressing any questions.

Clarifying Questions

DR. BATEMAN: Thank you. We will now take clarifying questions for Olas Pharma. Please use the raised-hand icon to indicate that you have a question and remember to clear the icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter if you can.

If you wish for a specific slide to be displayed, please let us know the slide number if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Dr. Meisel?

DR. MEISEL: Hi. Thank you. Steve Meisel with M Health Fairview in Minneapolis. I have a couple

of related questions to each other. First of all, specifically, you're proposing that only the 7 and a half milligram strength would be approved, correct? Norco, Vicodin they've got three strengths of 5, 7 and a half, and 10, but you're only asking for seven and a half. Is that correct? Norco, Vicodin, they've got three strengths of 5, 7 and a half, and 10, but you're only asking for 7 and a half? Is that correct?

MR. SCOTT: Yes. The Hydexor, the medication and the NDA contains 7.5 milligrams of hydrocodone, correct.

DR. MEISEL: As common sense, 7 and a half is a midpoint, though. Some people need more; some people can get by with less. In your clinical trials, did anybody require more than 1 tablet per dose?

MR. SCOTT: Yes. Thank you for your question, and I'll have Dr. Schachtel speak to this. But the short answer to your question is no, that's not how our trials were designed. Every dose was 7.5 milligrams, and it was fixed dose to have clear comparison with Norco.

This is the dose that's on the table right

now, obviously, the 7.5. We have other dosages in development, but the Hydexor, this particular formulation of Hydexor as you know is not for every patient or every physician. But to the extent a physician feels that this dosage and Hydexor is appropriate according to the label for their patient, they would administer it at that point. If it's the wrong dosage with respect to pain, Hydexor would not be the product at this time for them at this dosage. But because of the REMS program and the limitation of the inpatient, we do feel that when it is administered, it would be safe.

Dr. Schachtel, could you speak to that, the clinical program in the dosing?

DR. SCHACHTEL: Dr. Michna [sic], there's really nothing to add. They all received only 7.5 milligrams.

DR. MEISEL: The other clarifying question relating to this topic is Norco, Vicodin, you can take that up to 6 tablets a day, but you're only recommending 5 tablets a day. If a patient were to require a sixth dose, what are you suggesting that your

labeling tell physicians to do?

MR. SCOTT: Yes, thank you. Well, our label -- yes, correct -- it caps the dosing at 5. So after that, they would have to transition to another medication. Because our label has that limitation and they still required pain management and they required opioids, they would have to go back to Norco or an alternative.

DR. MEISEL: Okay. Finally, do you have any data that suggests that 12 and a half milligrams of promethazine is -- I don't want to say antidote, but effective anti-nausea dose for 7 and a half of hydrocodone, so that if a second tablet was required, they would 25 milligrams.

Is that sort of the equivalent or if you needed a second tablet, 12 and a half would be adequate as an anti-nausea product? And this may not be with the current label that you're recommending, but in the earlier trials that you base this on.

MR. SCOTT: Yes. I just want to make sure I understand your question. Is your question do we have data on the accumulation of any potential side effect

as we continue to dose or whether or not the efficacy of the promethazine, of the 12.5 with our tablet, remains efficacious?

DR. MEISEL: Well, I guess what I'm getting at -- and you're suggesting people don't take a second tablet, or a tablet and a half, or whatever, but certainly if they did, they would increase their exposure to promethazine. And I'm trying to understand whether in addition to the increase in side effect, whether they would get increase in benefit.

MR. SCOTT: I understand. So I'm going to have both
Dr. Gan speak to this from a practice perspective with respect to how he understands what the label is directing to do, and then also what we saw in our clinical trials from Dr. Schachtel. But first I'll go to Dr. Gan.

Dr. Gan?

DR. GAN: Thank you. Good morning, panel members. My name is TJ Gan. I'm a professor and chair at Stony Brook School of Medicine. I have an interest in this topic of postoperative nausea and vomiting, and

have been a lead author for PONV International Consensus, most recently published two months ago in Anesthesia and Analgesia. I receive honorarium from Charleston Laboratory.

To answer your question regarding the efficacy of 12.5 milligrams of oral promethazine, the data suggests that this dose is effective, as has also been shown by the two pivotal trials. We have conducted previous studies and found that the minimum efficacious dose for promethazine is 6.25 milligrams intravenously. As you know, there is no formulation for oral promethazine at 6.25. 12.5 is the lowest oral dose and has been shown to be effective.

Back to you, George.

MR. SCOTT: Thank you, Dr. Gan.

Dr. Schachtel, if you can approach it from a clinical perspective and what we saw in our study.

DR. SCHACHTEL: Yes. We did not study other dosages of promethazine, so I can't answer the question from that perspective. I'm sorry to say that's all I can answer.

DR. MEISEL: Okay. Thank you. That concludes

my questions.

MR. SCOTT: Thank you.

DR. BATEMAN: This is Brian Bateman. I have a question. The proposed label says that the medication should be used only when non-sedating alternatives are either not tolerated or ineffective, but we didn't hear in the patient journey, or in the briefing document when the patient's journey was described, an example of a trial of a non-sedating antiemetic.

So I'm just wondering how the sponsor foresees that criteria being met. How would it be established that a non-sedating alternative was not tolerated or ineffective?

MR. SCOTT: Yes. Thank you for your question, and I will have Dr. Gan address how this label will communicate to the clinician when Hydexor is appropriate and for what patient.

Dr. Gan?

DR. GAN: Sure. I will be happy to answer that question. There are a number of different antiemetics. Probably the one or two that are non-sedating, I would consider those are things like

drugs such as ondansetron, a 5-HT3 antagonist, and Aprepitant, which is an NK1 antagonist. All the other antiemetics come with its sedative properties.

The way I would see this product may potentially be used is in patients who have high risk for nausea and vomiting, and the consensus guidelines would recommend to give a patient prophylaxis antiemetics, and ondansetron and dexamethasone are probably two most widely used prophylactic antiemetics.

So in the postoperative setting, when the patient develops nausea and vomiting -- and we know from ample data that suggest that to repeat ondansetron does not work well. So in this context, one has to move on to another antiemetic. And in the context when the patient needs analgesia that is severe enough to require an opioid analgesic and have nausea and vomiting in the postoperative setting, and therefore is considered high risk, I would think that in this context, Hydexor, which has both an opioid analgesic and an antiemetic as a lowest dose of promethazine, would be recommended for that particular patient who are high risk and in a hospital environment under

continuous monitoring.

I hope that answers your question. Back to you, George.

DR. BATEMAN: Sure, but just to follow up on that, you're kind of describing a scenario where the patient already received ondansetron and dexamethasone and had nausea and vomiting. That's different than the label is proposing, where Hydexor would be given to patients at high risk for nausea and vomiting.

DR. GAN: That is correct. So typically, we don't give patients this drug -- I would not clinically use it preoperatively; I would use it postoperatively when the patient requires analgesia and is able to take oral pills. That is in that context I think this medication would be used clinically.

DR. BATEMAN: Okay. So we're going to move on, and then we will come back for additional clarifying questions later.

We're now going to move on to the FDA presentations starting with Dr. Roca.

FDA Presentation - Rigoberto Roca

DR. ROCA: Hello again. This is Rigo Roca,

and my colleague Dr. Tieu and I will be presenting the FDA perspective.

This is an overview of a presentation from this morning. I will briefly go over the regulatory history and touch upon the efficacy and safety, some of what you have just now heard by the applicant's presentation. I will comment on utilization data, and then Dr. Tieu will speak about the proposed REMS.

The original NDA submission was in 2016, and at that time, the indication was for the relief of moderate to severe pain while preventing or reducing opioid-induced nausea and vomiting. That submission received a complete response in January of 2017. During the second review cycle, which began in October 2017, the application was presented to the combined AADPAC-DSaRM committee, as was noted, in February of 2018.

The proposed indication was very similar to the original proposal with respect to preventing and reducing opioid-induced nausea and vomiting, but it's noted to be for short-term management of severe pain. Among the issues discussed in the advisory committee,

which you have also heard this morning, the committee noted that opioid-induced nausea and vomiting may decrease over time and that there was the potential for side effects not commonly described for other antiemetics. It was also noted that although the applicant demonstrated efficacy in the clinical trials, they have not adequately identified a patient population that predictably requires the proposed concomitant therapy as an analgesic and antiemetic.

The applicant received a complete response letter in April 2018, and during a post-action meeting held in May of that year, the applicant acknowledged the need to identify a patient population that requires Hydexor. They also proposed another modification to the indication to limit the number of days.

The division did not agree with the new indication being proposed because of concerns that many patients could be exposed to promethazine who did not appear to need an antiemetic. In a post hoc analysis conducted by the review team, it was noted that in an enriched population, approximately 30 percent of the patients in the comparative treatment group Norco

developed opioid-induced nausea and vomiting on day 1, and that the frequency decreased over the 5-day course of the study. It should be noted, however, that this and other post hoc analyses still demonstrated a treatment effect for Hydexor.

The discussions continued during this meeting and the following points were made. The applicant proposed to further limit the indication to post-surgical patients only and would consider additional text to other parts of the package inserts such as the contraindication, or warning and precautions, and the addition of a boxed warning. The applicant also noted that the product will be used on an as-needed basis and the proposed dosing regimen would further limit the number of tablets per day.

The applicant proposed that safety will be further assessed on a postmarking period through an observational study. The applicant also noted that the FDA analysis had excluded other clinically relevant presentations of opioid-induced nausea and vomiting that could be further analyzed from the secondary endpoint. And at the end of the meeting, it was agreed

that additional analysis could potentially identify the benefits of Hydexor, and that these analyses would be included in response to the second complete response letter.

Part of the reason I'm going through this regulatory history is because I think it will give you a picture of the different interactions that occurred since 2018 and today. This brought us to a third review cycle which began in August of 2018. This submission did not contain any [indiscernible] data, instead containing additional analysis in subpopulations of study CLCT-003, which you might recall was a study in post-bunionectomy patients.

The review team evaluated the additional analysis and concluded that the concern remained, the lack of a demonstration of patient population that can prospectively be identified as predictably requiring this product. The third complete response letter was issued in February 2019 with the deficiency as noted on the screen.

After receiving the third complete response letter, the applicant submitted a request for a formal

dispute resolution. In this request the applicant asked that the office director rescind the complete response letter and approve the product. At the end of the formal dispute resolution process, the applicant's request was denied.

Dr. Thanh Hai in her letter, which was included in the background package, noted that the division was to reconsider the applicant's proposed labeling revisions and consider revisions that would address the agency's concerns. She noted in her letter that the revision could further include restrictions on dosing, patient population, labeling claims, packaging, and distribution, which may require a REMS.

Now we are in the fourth review cycle. The submission was received in June of last year and contained a new proposed labeling and a REMS. The counter-proposal to the indications are on the screen and, as you noted, the applicant in their presentation presented the indication as well. As was described, this stipulates an adult post-surgical patient population that is at high risk of opioid-induced nausea and vomiting and a maximum number of days.

Additionally, limitations of use are included as noted here on the screen and as described by the applicant.

I'm only going to very briefly remind the committee that the application contained the results of two studies that demonstrated the efficacy of Hydexor. One was in the post-dental surgery patients and one was in post-bunionectomy patients as you heard earlier this morning. The efficacy was not in question before, nor is it now, and therefore I will not comment further.

With respect to safety, the safety profile of the combination product, hydrocodone/acetaminophen, and promethazine are well known and have been in clinical use for many years. In addition, the safety profile of the proposed combination product has also been well characterized and discussed the previous advisory committee.

Touching briefly on drug utilization information, as part of the NDA review, our colleagues in the Office of Surveillance and Epidemiology evaluated drug utilization data to provide context and background information for the components of Hydexor. This graph shows the nationally estimated number of

patients with a hospital discharge billing for hydrocodone and acetaminophen and promethazine on the same day in U.S. non-federal hospitals.

As shown by the gray bars, the total number of patients with concurrent use has declined. We further stratified the data by location of care to understand these drug components that have been administered within the hospital. As shown by the colored line, overall, the number of patients with concurrent use has declined in all locations of care in our study period, with about half of those patients spending some time in the operating room.

I will now turn the presentation over to Dr. Tieu from the Division of Risk Management.

FDA Presentation - Carolyn Tieu

DR. TIEU: Thank you, Dr. Roca.

My name is Carolyn Tieu. I'm the acting team leader in the Division of Risk Management at the FDA. I will now discuss the risk management for Hydexor. During this presentation, I will provide a brief overview of the regulatory authority for risk, evaluation, and mitigation strategy, also known as

REMS. I will briefly review the safety issues of Hydexor, which you have heard about in detail earlier. Finally, I will discuss the current risk management proposal.

First, I will discuss the REMS overview. A REMS is a drug safety program that can be required by the FDA for certain drugs. A REMS is designed to mitigate serious risks associated with the drug. It includes strategies beyond labeling to ensure the benefits outweigh the risks of the drug.

The FDA Amendments Act of 2007 gave the FDA authorization to require applicants and application holders to develop and comply with REMS programs if it is determined necessary. The FDA has the authority to require a REMS pre- or post-approval. If the FDA determines a REMS is necessary, the REMS components can include a medication guide or a patient package insert; a communication plan for healthcare providers; certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose; elements to assure safe use, which may restrict distribution; and an implementation system. REMS must include a

timetable for submission of assessments.

If elements to assure safe use is determined as a necessary component of REMS, the elements to assure safe use can include the following: certification and/or specialized training of the healthcare providers who prescribe the drug; certification of pharmacies, practitioners, or healthcare settings that dispense the drug; limited settings for dispensing or administration of the drug such as a hospital setting; having each patient using the drug be subject to certain monitoring; drug is dispensed/administered only with evidence of safe-use conditions, for example, a pregnancy test or enrollment of treated patients in a registry.

These elements may be used in combination to create a specific risk mitigation program. Additionally, elements to assure safe use must align with the specific serious risks listed in the labeling. They cannot cause undue burden on patient access to the drug, considering in particular patients with serious or life-threatening diseases or conditions and patients who have difficulty accessing health care.

Now I will provide a summary of the risk management issues raised during the advisory committee on February 14, 2018. At the time of this advisory committee, the applicants proposed indication was for short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting.

The treatment would be less than 14 days with the dosing schedule of 1 tablet every 4 to 6 hours as the maximum daily dosage. The use of this product would have included both inpatient and outpatient treatment of pain and prevention of opioid-induced nausea and vomiting.

Hydexor was proposed to join the Opioid Analgesic REMS, also known as the OA REMS. The OA REMS is required for products intended for opioid analgesics used in the outpatient setting and not covered by another REMS. The OA REMS is an educational effort and one of a number of national efforts that are designed to address the epidemic of prescription opioid abuse by educating prescribers and other healthcare providers on the treatment and monitoring of patients with pain.

The applicant also proposed packaging that would contain product for 3, 5, or 7 days of therapy that would be in child-resistant blister packs and an opioid buyback program, which would allow patients to return unused tablets for disposal. Collectively, the applicant believed that these strategies would reduce the number of unused tablets available for abuse, misuse, and diversion.

Members at the advisory committee expressed concerns about the intended use of Hydexor in a broad patient population and the duration of use of up to 14 days since the patients studied in the clinical trials were postoperative. Despite this being an enriched population, not every patient experiences opioid-induced nausea and vomiting.

The members were also concerned about the lack of dosing flexibility with a fixed-dose combination formulation that would expose patients to unnecessary side effects of promethazine when it is not needed; for example, a patient may need pain medicine but not an antiemetic.

There were also concerns about the lack of

data on the risk of sedation and drop in blood pressure in the elderly population and patients age 65 and older and the proposed drug packaging that may encourage patients to finish the package when Hydexor should only be used as needed. Furthermore, there were limited details on the proposed buyback program implementation. Most committee members did not believe that the applicant's proposed risk management strategies for Hydexor were adequate.

After the advisory committee, the agency communicated to the applicant in the second complete response letter the need to better identify the patient population that would require concomitant therapy with an opioid and a pre-emptive antiemetic for opioid-induced nausea and vomiting, as the fixed-dose combination would expose many patients to additional risk with no added benefit.

The agency also had concerns about the risk of CNS depression, particularly with the combined use of an opioid analgesic and promethazine, and that the risk of excessive sedation may result in falls or other accidents. Since Hydexor includes an opioid, there is

also the risk of life-threatening respiratory depression, addiction, abuse, and misuse.

This then now leads us to the applicant's current risk management proposal. This table is the summary of how the applicant has addressed some of the AC's concern with the current submission. Initially, the applicant had proposed the use of Hydexor in a broad patient population with a duration of use of up to 14 days.

With this submission, the patient population would be narrower since it would be indicated for patients experiencing acute postoperative pain severe enough to require an opioid analgesic for a maximum of 3 days who are at high risk for nausea and vomiting.

There was a lack of data on the risk of sedation and drop in blood pressure in the elderly population. To address this concern, the applicant is proposing a limitation of use to state that Hydexor should only be used when non-sedating alternatives are either not tolerated or ineffective. Additionally, Hydexor should not be used in skilled nursing facilities, as patients are likely to be older and more

at risk for respiratory depression and falls due to excessive sedation.

The other previous concerns include the drug packaging for 3, 5, or 7 days of therapy and the drug buyback program. The applicant is no longer proposing this packaging or the drug buyback program, as Hydexor will only be used in certified medically-supervised settings such as hospitals and surgical centers and not for use in a home setting.

The applicant proposed a REMS to ensure the benefits of the drug outweighed the risks. As mentioned previously, elements to assure safe use must align with a specific serious risk listed in the labeling. Therefore, the proposed REMS goal is to mitigate the risk of life-threatening respiratory depression and the risk of falls or other accidents resulting from excessive sedation by ensuring that Hydexor is dispensed only to patients in certified medically-supervised healthcare settings.

The REMS components include elements to assure safe use; implementation system; and a timetable for submission of assessment reports. The elements to

assure safe use would require healthcare settings that dispense the drug to be certified. This REMS would also limit administration only to certified medically-supervised settings such as hospitals and surgical centers.

The certified healthcare settings that dispense Hydexor must establish policies and procedures to manage acute opioid overdose, including life-threatening respiratory depression; have fall precaution protocols on site; discontinue Hydexor after 3 days of use; and verify that Hydexor is not dispensed for use outside of the certified healthcare setting.

The current assessment plan for this REMS is under review, however, the assessment plan may include metrics to capture data on REMS implementation and operations; REMS enrollment and utilization; REMS infrastructure and performance; compliance and audit; and surveillance data on adverse events of special interest, more specifically the risk this REMS is intended to mitigate, which is the risk of respiratory depression and the risk of falls or other accidents resulting from excessive sedation.

If Hydexor is approved, the FDA believes that the proposed REMS will address the safety concerns raised previously by the AC by ensuring that patients are only administered Hydexor in a certified medically-supervised. Hydexor will be administered only for a limited time where patients can be monitored for respiratory depression and the risk of falls or other accidents resulting from excessive sedation.

By limiting Hydexor to postoperative use, specifically in hospitals and surgical centers, the risk of abuse, misuse, and addiction would be mitigated in outpatient settings since patients would not have access to tablets in their home. Additionally, because this is in a medically-supervised setting, prescribers can determine if Hydexor should be discontinued due to intolerance of side effects or changes in a patient's analgesic and antiemetic needs.

Finally, the applicant will be required to submit REMS assessment reports to determine the effectiveness of the REMS to ensure that Hydexor is only used in healthcare settings that are certified in the REMS. This concludes the FDA presentation. I will

now turn it over to the chairperson.

Clarifying Questions

DR. BATEMAN: Thank you.

We will now take clarifying questions for FDA. Please use the raised-hand icon to indicate that you have a question and remember to clear the icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and to direct your question to a specific presenter if you can.

If you wish for a specific slide to be displayed, please let us know the slide number if possible. Finally, it will be helpful to acknowledge the end of your question with a thank you, and the end of your follow-up question with, "That's all for my questions," so we can move on to the next panel member.

We have about 10 minutes scheduled for clarifying questions, so if I could ask everyone to just have one-part questions. Please don't ask multiple-part questions at this point.

Dr. Hincapie-Castillo?

DR. HINCAPIE-CASTILLO: Hi. This is

Dr. Hincapie-Castillo from UF College of Pharmacy, and this question is for Dr. Roca. In slide A, you mentioned that the approval would be accompanied by a postmarketing observational study to further assess safety. Can you please comment whether this would be optional or required, and what would be some of the outcomes that would be in this postmarketing study? Thank you.

DR. ROCA: Hi. This is Dr. Roca. I do believe that the slide you're referring to was what they had originally proposed. This was something that the applicant had proposed earlier on. So my understanding is that that is not on the table right now, but we can certainly ask the applicant later on. But the slide that you're referring to was what was originally proposed.

DR. HINCAPIE-CASTILLO: Thank you. That is all for my question.

DR. BATEMAN: Dr. Nelson?

DR. NELSON: Yes. Hi. It's Lewis Nelson from Rutgers. I guess this question is for Dr. Tieu. Given that we've seen some even fairly ironclad REMS have

workarounds applied to them, such as the TIRF REMS for transmucosal products, which were originally meant for breakthrough cancer pain, get utilized for chronic pain.

In one of your slides you talked about the sponsor requiring some assurance that the pills will not be given to the patient, otherwise dispensed outside of a care setting. What is the mechanism will you be able to monitor that? I guess the sponsor might want to clarify, when they have a moment, how they plan to do that if you don't know. Thank you.

DR. TIEU: Hi. This is Dr. Tieu. I'm going to turn this over to our division director, Dr. LaCivita, to comment on your question.

DR. LaCIVITA: Hi. This is Cynthia LaCivita with the FDA. In preparing for this AC, I did go back and look at a number of the more recent REMS reports, assessment reports for REMS that include elements to assure safe use, this particular element that the drug can only be dispensed in certain healthcare settings.

These REMS of course cover products that have various formulations and different indications, so some

do require -- some may slightly differ. But based on these reports received, and the ones that the agency has completed our reviews on, limiting use to certain healthcare settings is working as intended by restricting the use to only the REMS in the certified healthcare settings.

In addition to the data submitted often by the sponsors, the agency also looks at other data sources to see if the REMS are being dispensed outside, outpatient settings. For most programs that are similar to the Hydexor REMS, the databases have not detected outpatient dispensing such as in retail pharmacies or other long-term care settings.

We also look at other databases to detect accidental exposure, misuse, and abuse, and although there are some substantial limitations with these databases in identifying specific products involved in these events, at this time we haven't identified concerns for products under the REMS that are most similar to Hydexor. The TIRF REMS is somewhat different. This is really restricting it to certified healthcare settings, and more than likely we would

follow the same thing for Hydexor. I hope that answers your question. I'm done.

DR. NELSON: Thank you. Yes.

DR. BATEMAN: Dr. McCann, we see that you have your hand raised but you're not connected to audio So if you can recall into the meeting, that would be great.

Dr. Zaafran?

DR. ZAAFRAN: Yes. Thank you. One of the questions I had for the FDA, when looking at the medication using the REMS, has anybody evaluated or looked at the cost, the additional cost, of providing care to a patient under these conditions for something that is fairly basic if given individually? Thank you. That's my question.

DR. LaCIVITA: Hi. This is Cynthia LaCivita. I'm with the FDA. We have not looked at the costs associated with implementing such a REMS. We look at the safety issues that are concerning the REMS or concerning the risks associated with the product.

DR. BATEMAN: Okay. We'll go back to Dr. McCann.

DR. McCANN: Hi. My question originally was for the sponsor but maybe the FDA could also answer it. I guess this is not supposed to be used in skilled nursing facilities, but a lot of rehab hospitals are also part of skilled nursing facilities. So is there a possibility that this drug would be used in the rehab hospital portion of the skilled nursing facility? Thank you.

DR. ROCA: Hi. This is Dr. Roca.

Dr. Bateman, I think that actually is a question more for the sponsor, but I don't know if you want them to answer now or wait until later on. I'll leave it up to you.

DR. BATEMAN: Why don't we wait until after the open public hearing?

DR. McCANN: Alright. Thank you.

DR. BATEMAN: So we'll move on to Dr. Sprintz.

DR. SPRINTZ: Hi. This is Dr. Michael Sprintz, and I have a question. I think it would be either for Dr. Tieu or Dr. LaCivita regarding slide number 30. The question that I have is you have the proposed labeling indicated only for management in a

certified facility, but there are so many times where you have ambulatory surgery centers, which are technically certified and then the patients are discharged.

How does this REMS prevent the dispensing either from a hospital pharmacy to a patient upon discharge or from a nurse to a post-op patient upon discharge in which they're going to be under the influence but on their way home? How are they going to enforce that? Because I noticed that the labeling did not -- at least as it's written in the first upper-right box doesn't state specifically for inpatient only. So that's my question.

DR. LaCIVITA: Hi. This is Cynthia LaCivita with the FDA. I apologize. It takes me a second or two to get off mute sometimes.

Typically, what we do for these type of REMS, we look at issues of non-compliance. Of course for the certified healthcare settings you'll have to have an authorized representative that would ensure that the policies and procedures are in effect and being followed within their institution, but program

compliance is typically measured through the adherence to the REMS requirements and also through audits.

Non-compliance has also been detected through call centers. Sometimes non-compliance is self-reported by the site, as the site realizes that they've made an error. The audits will be one way for us to follow this, and certainly if there are issues with non-compliance, there is a corrective action and preventive plan, or a CAPA, that is implemented. These are intended to eliminate further reoccurrence of such non-compliance. The remedial actions typically vary anywhere from re-education to deactivation of a site.

DR. SPRINTZ: So it's not the sponsor's responsibility in any way to do that, correct?

DR. LaCIVITA: That is correct. When the authorized representative agrees to the conditions of the REMS, then that is their responsibility to ensure that occurs.

DR. SPRINTZ: I see. Alright. Thank you.

DR. BATEMAN: This is Brian Bateman. I have a question for Dr. LaCivita. I'm wondering about this component of the label should only be used when

non-sedating alternatives are either not tolerated or ineffective. Would that be a component of the REMS that was enforced, and if so, how do you envision that being enforced?

DR. LaCIVITA: This is Cynthia LaCivita again from the FDA. The REMS is going to mitigate the risk of life-threatening respiratory depression and risk of falls or other accidents that occur due to excessive sedation. The clinical decision to use the product is going to have to be made at the medical level, but once the product is being used, we want to mitigate the risks of the respiratory depression and falls or other accidents from excessive sedation. So that would require the fall precautions to have the ability to manage acute overdose and so on.

Does that answer your question, sir?

DR. BATEMAN: Yes, I think so. So this would be a recommendation in the label, but ensuring that it is only used when alternatives are not tolerated or ineffective wouldn't be a component of the REMS per se.

DR. LaCIVITA: Right.

DR. BATEMAN: Okay.

Dr. Nelson, you still have your hand up. Do you have a second question?

DR. NELSON: No. I'm sorry. I didn't put it down.

DR. BATEMAN: I think we will now take a 10-minute break. Panel members, please remember there should be no chatting or discussion of the meeting topics with other panel members during the break. We'll reconvene at 11:10.

(Whereupon, at 11:01 a.m., a recess was taken.)

Open Public Hearing

DR. BATEMAN: We will now begin the open public hearing session.

Both the FDA 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, 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 relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your participation in the meeting.

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issue before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with

dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce yourself? Please state your name and any organization that you're representing for the record.

DR. ZUCKERMAN: Thank you. I'm Dr. Diana Zuckerman, president of the National Center for Health Research. Our nonprofit center scrutinizes the safety and effectiveness of medical products, and we don't accept funding from companies that make those products.

My expertise is based on postdoctoral training in epidemiology and as a former faculty member and researcher at Vassar, Yale, and Harvard. I've also worked at HHS, the U.S. Congress, and the White House, and I'm on the board of the Alliance for a Stronger FDA, which lobbies for more appropriations for the FDA.

I'm going to focus today on two issues, risks versus benefits and REMS. FDA requires evidence that drugs are safe and effective, defined as having benefits that outweigh the risks for most patients.

And for all opioids, REMS are crucial to reduce the known risks.

Nausea is terrible and Hydexor reduces it. But Hydexor's efficacy for pain, as I understand it, was compared to placebo, not to less risky pain treatments. Yet, research has shown that non-opioid pain meds can be as effective as opioids in some settings.

The REMS proposed today are very impressive. FDA has depended on REMS to reduce the risks of opioids, but unfortunately those REMS have been ineffective. Just a month ago, the inspector general of HHS released a scathing report about this, but FDA had previously criticized opioid REMS four years ago.

The IG report focused on whether FDA held sponsors accountable for evaluating REMS and whether there was evidence that the REMS for opioids were effective. The IG report criticized the sponsors and the FDA for the lack of data on whether REMS truly worked, but two of their findings seem especially relevant to this meeting. Quote, "Some opioid manufacturers engaged in deceptive marketing practices

that undermined the REMS educational messages regarding risks," and quote, "FDA has limited authority to enforce manufacturers' compliance with their REMS."

I'm going to briefly show results from an evaluation of REMS that FDA provided to this advisory committee in 2016. FDA reported that the analysis of an online REMS training program to ensure correct prescribing of opioids showed 48 percent of physicians who took the training said they didn't change their prescribing habits; only 49 percent of the physicians used the patient counseling document that FDA had put together; and most physicians didn't know about REMS training.

The fundamental issue for me is whether sponsors have an incentive to follow through on their REMS commitment, and this is true for all sponsors, because let's face it, better training will reduce prescriptions, alternative pain management therapies will reduce prescriptions, and a 2017 Boston Medical Center study found that the FDA blueprint for prescriber education failed to provide prescribers with adequate information.

Most physicians didn't take the training, but what about those that did? My next four slides are pie charts that will show some key information that physicians were supposed to learn. The first pie chart -- thank you -- is up, and it shows that 1 in 3 physicians did not learn how to assess patients for opioid treatment.

This slide shows that 83 percent of the physicians taking the course did not learn what was supposed to be taught about initiating, modifying, or terminating opioid treatment; this slide shows that one-third did not learn general drug information about opioids; and this last pie chart shows that two-thirds did not learn specific product information that they were supposed to have been taught.

In summary, there's clear evidence that opioid REMS have not worked in the past, and you've heard about some of the concerns about them already today. So I'm encouraging you to encourage the FDA to not approve an opioid that has not even been studied for efficacy compared to non-opioid pain meds, with clear concerns about whether the REMS, which as I said, are

very impressive as they've been proposed, but no clear evidence that they can be enforced. Thanks very much.

DR. BATEMAN: Thank you.

Speaker number 2, your audio is connected now. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. COLLIGNON: Good morning. My name is Dr. William Collignon. I'm a private practice general surgeon and have been in practice for over 35 years. I have no financial interest in Hydexor, nor am I being paid for my comments by any organization or sponsor.

I've mentioned I've been in practice for over 35 years, and my surgical experience includes basically all types of general surgery, including breast surgery, most abdominal surgeries such as cholecystectomies, colon resections, et cetera, as well as trauma such as motor vehicle accidents and gunshot wounds. As such, I have extensive experience in postoperative acute pain management.

I have used the medications that are included in Hydexor in combination for years in the hospital

setting and have found them to be very effective. People not only have pain, but they also have nausea, and we practicing physicians often use a combination of medications such as Demerol and Phenergan or hydrocodone and Phenergan for acute postoperative pain. I agree that transition to non-steroidals, et cetera, to prevent opioid addiction is very important, and I try to do that, including regional blocks, et cetera, when we can do that.

But having hospital settings write a couple of different medications to control pain and nausea increases the workload on the hospital staff. It often causes duplicate orders, and I'm concerned at times for errors being generated this way. It seems to me that a combination medication where one script would work fine would cut down on this and also achieve treatment for both pain and nausea in the acute care setting.

Hydexor would seem to be very beneficial, to me, for my patients to treat both conditions at the same time. I appreciate being allowed to comment.

DR. BATEMAN: Thank you.

Speaker number 3, your audio is connected now.

Will speaker number 3 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MS. PARKS: Good morning. My name is Gina Porcelli Parks. I'm a licensed nurse practitioner, and I've been providing health care to women of all ages since 1989 in the specialties of obstetrics and gynecology. I would like to thank the FDA and the advisory committee for allowing me the opportunity to share my evidence on nausea and vomiting as not only a healthcare provider, but more importantly a recent breast cancer survivor.

For full disclosure, I don't have any financial interest in the outcome of this meeting. I've not been paid by any organization or sponsor for my time, thoughts, or my real-world evidence related to nausea and vomiting for this critical public meeting and its potential effect on the approval of the novel, first-in-class combination product by the brand name Hydexor.

As many of you are aware, women are at a high risk for nausea as outlined in the Fourth Consensus

Guidelines for the Management of Post-Operative Nausea and Vomiting. For the last 31 years, I have cared for patients who have undergone a multitude of surgical procedures, including cesarean sections, hysterectomies, myomectomies, oophorectomies, and a host of vaginal and urologic procedures, including eight years working with gynecologic oncology patients with advanced cancer.

They say that experience is the best teacher in life, and little did I know that this statement would come full circle for me later in my career. As a licensed nurse practitioner, I have advanced skills that allow me to diagnose conditions, prescribe medications, and manage patients' overall care. I have hospital privileges, and I'm in the hospital about 5 to 10 days a month.

My time in the hospital is split between managing patients' overall care who are recovering from surgery and often as a surgical assistant on more difficult procedures. Mostly all my patients require pain medications following these procedures, which lead to our most common complaint of nausea and vomiting.

We have standing orders for antiemetics and use promethazine quite regularly. I get complaints of nausea with the majority of patients, probably about 70-80 percent, who undergo these very difficult procedures.

As the times have changed, the length of hospital stay has also changed, and many surgical procedures have decreased their hospital stay from about 5 days to possibly 2 days or less, and in some cases people are going home as outpatients from hysterectomies. This change has increased how hard hospital staff must work to control nausea and vomiting so patients are able to rest and recover. Patients rest and recovery are the number one goal during this critical period so acute pain doesn't turn into chronic pain.

Nausea can often lead patients to retch. Retching, which is an unpleasant sensation of vomiting without vomiting, can become more serious by causing dehydration and potentially damage to recent surgically repaired tissue and organs. In addition, nausea and vomiting also affect patients' ability to rehab, and

often if they're able to be discharged.

When patients remain stationary as a result of nausea, things such as blood clots and pneumonia can adversely affect the patient's recovery. Simply put, nausea is a major problem in both the inpatient and outpatient setting that for some reason is so commonly overlooked until it happens to you or someone close to you. I believe there's been a desensitization to just deal with nausea in these settings because it's such a common event. It almost seems like we've adopted the, "Oh, well, if it doesn't kill you" perspective.

I began to follow Hydexor's story when the company relocated to their corporate headquarters in Jupiter, Florida about six years ago and became immediately intrigued because they were working on something novel and new for patients who suffered from opioid-induced nausea and vomiting. I'm not aware of any other company who has focused on this unmet need for patients.

Hydexor is a step in the right direction for a significant population of nausea patients who not only suffer from postoperative nausea from the surgery or

anesthesia prior to oral ingestion of an opioid, but also a useful option for those patients who have transitioned to recovery to prevent the nausea from occurring. I am passionate in the belief that patients should not have to prove their need for an antiemetic when we know it's an expected part of taking hydrocodone or any other similar product.

As I mentioned earlier in my presentation that experience is the best teacher, in February 2020, I was diagnosed with triple negative stage 3 metastatic breast cancer. My horrible bouts with nausea were a direct intersection with every single one of my patients' complaints of nausea. While bravely fighting this horrible disease, it put nausea and vomiting squarely back in front of me, not as a healthcare provider, but now as a patient.

DR. BATEMAN: If I could ask you to wrap up your comments. The time's expired.

MS. PARKS: While resting at my bedside following my bilateral mastectomy and axillary dissection, nausea was the last thing I wanted to deal with while trying to be brave, strong, and composed to

beating this nasty beast of a disease. During that time at the hospital and as an outpatient, I reflected on how debilitating nausea is and remains, given healthcare providers best attempts. There are times that providers have to manage the symptoms of nausea and vomiting, but nausea can also be something that could be controlled, and more importantly, prevented.

In closing, I want to commend all the committee members and acknowledge that you're all in a very difficult position to be voting on, not just another opioid, but a new opioid combination that serves as the first for patients who suffer from opioid-induced nausea and vomiting. Thank you --

DR. BATEMAN: Thank you for your comment.

MS. PARKS: Um-hmm.

DR. BATEMAN: Speaker number 4, your audio is connected now. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MS. McKINNEY: Good morning. My name is Deandra McKinney. I would like to thank the advisory committee and the staff at the FDA for allowing me to

have a voice today that supports innovation for opioid-induced nausea and vomiting at this public hearing. I have no financial interest in the results of today's meeting, nor have I been paid by any company or organization to speak at today's open public hearing related to Hydexor.

I am a proud military veteran having served in the United States Army for four years. I currently hold a master's degree in criminal justice and a PhD pending in justice administration and leadership with Capella University. I am currently employed as the principal and academic manager for Horizon Youth Services, a contractor for the Department of Labor in Simpsonville, Kentucky. Whitney M. Young Job Corps is a trade school that offers high school diploma attainment as well as certifications in various trades such as welding; brick; cement; HVAC; CNA; pharmacy tech; certified medical assistant; and culinary arts.

In the past, I have worked at the University of Louisville, the adult psychiatric unit, as a licensed practical nurse. I became interested in Charleston's drug CL-108, now known as Hydexor, a few

years ago while doing research on new medical treatments or advancements pertaining to nausea and vomiting.

Nausea is a common symptom of many disorders that I have dealt with as a patient while working as a licensed practical nurse, as well as overseeing the healthcare certifications we offer here at Job Corps. I was disappointed that Hydexor wasn't approved in 2018 and had always hoped that the company and others would continue their quest to innovate this underserved and unmet patient need.

I was diagnosed with gestational diabetes during my pregnancy in 1990, which resulted in full-blown diabetes soon after. After many years of managing diabetes through diet and exercise, oral medication, and then insulin, my kidneys failed in 2010. I was devastated because I had so much life to live and so many things that I wanted to accomplish. I was immediately placed on dialysis and I received that treatment modality for seven years. But by the grace of God, I was not only placed on a kidney transplant list, but also a pancreas transplant list that I

ultimately received in 2017.

I know the majority of the healthcare professionals and experts in this room understand the rigor involved in the workup leading to a transplant, but for those who do not, let me tell you, it is very intensive. During the screening process, it was discovered that I had a blockage in my heart, and in order to even continue to be considered for the kidney-pancreas transplant, I had to undergo open-heart bypass surgery to repair it.

All surgeries are tough on patients when it comes to postoperative pain control, but open-heart surgery is one of the most difficult ones to recover from, at least it was for me. I was in excruciating pain, and this began a time period where I was faced with nausea and vomiting regularly as a result of my surgeries and pain treatment.

As a heart bypass post-op patient, I was started on IV morphine. My doctors tried their best to treat my post-op nausea and ultimately control it with IV promethazine. As soon as I was moved to oral hydrocodone, it caused me to become even more

nauseated, and I would throw up uncontrollably. Because nausea had set in, I was unable to keep oral antiemetics down. I believe I would be a patient that a physician would deem a high risk for nausea, and Hydexor would have replaced my oral hydrocodone while in the hospital.

I am proud to be in front of you today as a double-organ transplant survivor. I was able to meet all the pre-transplant medical requirements such as my open-heart surgery. I experienced the same problems with nausea and vomiting during my post-op recovery following my kidney-pancreas transplant.

I want to also mention to the committee that my nausea continued with almost every dose of pain medication through the duration of my recovery. I don't recall if anyone has yet to discuss the unpleasant or unpopular topic of antiemetic suppositories, but they are quite common, and I've used them because I was unable to prevent nausea and vomiting.

Before I close my speech today, I have read many articles, reports, and patients' testimonies in

regard to the opioid healthcare crisis, and one really struck a chord with me because it made me realize how difficult this committee's job is. In summary, this patient speaks on 35 years of dealing with chronic pain. The new regulations have altered their pain control that leave many patients like them with real unmet medical needs on the outside looking in.

Prior to this meeting, I have tried to put myself in the committee's shoes of being asked to vote on a new opioid. Hydexor is an opiate that has not contributed to the crisis, and I believe it should be looked at as replacing hydrocodone products for those patients whose physician in the hospital feels they are high risk for nausea and vomiting.

DR. BATEMAN: Can I ask you to wrap up, please, the last comment?

MS. McKINNEY: Yes.

DR. BATEMAN: Thank you.

MS. McKINNEY: I believe Hydexor is a step in the right direction for all patients who suffer from opioid-induced nausea and vomiting. Thank you for your time and consideration.

DR. BATEMAN: Alright. Thank you for your comments.

Speaker number 5, your audio is connected now. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. WOLFE: I'm Dr. Sidney Wolfe, the health research group of Public Citizen, and I have no financial conflicts of interest. Today's main focus is to decide whether previous safety concerns, which were reviewed quite thoroughly I think before, would be adequately addressed through a labeling change and REMS.

The second thing I'd like to talk about is the review of safety concerns from February 2018, the advisory committee. I've went through the transcript and looked up certain things that I don't think have been presented today; third, the company response to the 19 to 2 advisory committee vote against Hydexor approval, the same two advisory committees here today, some of whom aren't the same people; and FDA's response to the company's criticism and, briefly, current FDA

comments, which Dr. Roca went over before.

The question for the vote is, "Would the proposed labeling and a REMS alter the inherent previously documented harm-benefits ratio of Hydexor?" The drug stays the same. The cautions in the form of labeling change and REMS, which I'm concerned about how well they would work, are the only difference.

In the review of the safety concerns from the February meeting, most people agree that a fixed-dose combination limits the ability to tailor the dose of the drug based on an individual's needs, thus reducing clinical flexibility. Some noted that the risk of adverse events and unintentional overdose associated with promethazine in the combination product outweigh the little benefit shown in the data.

The majority agreed that Hydexor poses greater risk than currently marketed hydrocodone/acetaminophen products. This is just because of the added CNS depression effect of promethazine. Some added that the proposed fixed dose combination includes 7 and a half milligrams of hydrocodone, which is higher than the usual starting dose of the drug for many people.

This is from the transcript. Dr. Steve Meisel, who sounds from his question like he's there today, said, quote, "We're asking people to take a drug to prevent the side effect of another drug but in itself is causing more side effects than promethazine. And pretty soon we'll have another drug proposed to us that will mitigate the adverse effects 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."

This is the response by Olas to the advisory committee meeting in their letter. This is quoted by the person in the FDA who denied their appeal to the decision, quote, "The negative vote was largely a result of --" and this is Olas' response -- "a philosophical bias against fixed-dose combinations," end quote, "and did not constitute --" again what the company said -- "a significant scientific development with selected quotes of committee members who voted against approval."

"The quotes you provided --" again, FDA writing to the company -- "could be deceptive and

interpreted as a philosophical bias against FTC products or a weighing of benefit-risk with the latter, the risk exceeding the former. Selective highlighting of texts from the transcript can result in different conclusions on the rationale behind a vote.

"Finally, a philosophical concern does not exclude the possibility that a vote was based on weighing of the benefit to risk of Hydexor. The two, a philosophical position and a benefit-risk conclusion, are not mutually exclusive."

The next slide from the same letter from the FDA to the company, quote, "The negative advisory committee vote clearly shifted the division's position. I do not consider that change in position --" which was described by Dr. Scott earlier -- "to be evidence of the division reneging on agreements laid out at the open advisory committee meeting, but rather a further re-weighing of benefits and risks based on the external expert advice provided by the advisory committee."

These are just current comments from the briefing packets for today's meeting, the director's memo, "The applicant did not identify a patient

population that predictably requires concomitant therapy within an analgesic and a pre-emptive antiemetic, with every dose to warrant exposure to promethazine."

"Although phase 3 clinical trials were enriched to enroll a population at risk for OINV, a substantial number of patients treated in the control, the hydrocodone and the Norco group, did not develop OINV. Can an appropriate population be identified for the safe use of this product? The applicant is redressing this concern through revised labeling and the proposed REMS."

"Would the proposed labeling and REMS alter the inherent previously documented harm-benefit ratio of Hydexor?" This is my paraphrasing slightly what the question is to the labeling change. The FDA accurately states, quote -- this is not just today but often -- "We regulate drugs, not doctors." And that's legally and technically correct.

"Even if companies do not violate prohibitions on off-label advertising, it is likely, if not certain, that off-label prescribing will occur, as with all

opioids and many other drugs."

"Given the increased harms of adding promethazine and failure to identify a patient population that predictably requires concomitant therapy with an opioid analgesic and a pre-emptive antiemetic with every dose to warn exposure to promethazine, overuse is guaranteed."

The other component beyond the labeling changes, again, the point I was making before, is that off-label prescribing, even with the program that's been mentioned today, is almost guaranteed.

The proposed REMS, this optimistic program to mitigate risk has not been successful as evaluated by the FDA for another opioid. During an August 3, 2018 meeting of your same two committees, data presented by the FDA revealed the failure of the transmucosal, immediate-release fentanyl, the so-called TIRF REMS, the most rigorous such opioid REMS safety program ever created, at least to date.

The TIRF REMS was created to provide safe use of TIRF products by limiting the prescribing of them to breakthrough pain and cancer patients and to ensure

that because the inherent risk of these potent drugs, only opioid-tolerant patients would be prescribed these products. Subsequent FDA analysis demonstrated that this REMS mitigation had not been effective. It was being prescribed to a lot of people who didn't have cancer pain, and as you know, it was being prescribed to people who were opioid naive.

I think this is worth mentioning. Dr. Nelson's question also mentioning the problems, serious problems, with the TIRF was responded to by the FDA in saying that this drug, Hydexor, would only be prescribed in certified medical settings.

This brings up the question about the two clinical trials that were in postoperative dental surgery patients and postoperative bunionectomy. It is unlikely, if those are typical of the kinds of patients that would be prescribed the drug, that they would stay in a certified medical setting, a dentist clinic, which is I suppose a certified medical setting, or an outpatient surgery center.

Imagine people with either of those problems staying there for 3 days so that the dispensing was in

a certified medical setting. More likely -- and that can be discussed later -- is that the 15 pills would work for 1 day, 5 pills a day, and then the patients would probably not be staying at a dentist's office or an outpatient surgical center for two other days. So they would really be tending in the direction of the same kind of problems that existed with the TIRF, and we would have, again, a serious doubt that the proposed REMS would work, just as the labeling change would not work because of off-label use.

It is highly unlikely that previously documented safety concerns can be alleviated by more limited labeling and a REMS program. Secondly, the combination of hydrocodone with another central nervous system depressant, promethazine -- and is why the added drowsiness occurred when promethazine was added -- being prescribed for large numbers of people, who will not get any benefit from promethazine, guarantees a serious risk of harm without any advantage for those patients.

I am hopeful that your advisory committee, in coordination with the ever-increasing public health

focus of the FDA, will make the right decision. Thank you very much. I appreciate the time to present today.

DR. BATEMAN: Thank you.

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

So we have about 15 minutes, before we take up the question, for additional clarifying questions, but before we do that, Dr. LaCivita wanted to provide some clarification on some points raised during the open public hearing.

DR. LaCIVITA: Thank you. This is Cynthia LaCivita from the FDA, and thank you for the opportunity for a point of clarification. Although this AC is not intended to discuss other REMS, I just wanted to comment that that OIG report was specific to the opioid analgesic REMS and the TIRF REMS program, and to note that the elements in the REMS are different than what is being proposed for Hydexor.

The requirements for these REMS are in the public domain, and the OA REMS makes training available to healthcare providers as a voluntary educational program for healthcare providers, as most of you on the panel are aware of. The approved REMS for the TIRF's elements require training for prescribers and pharmacists. The proposal for Hydexor is using a slightly different element. It's dispensing only in certified healthcare settings. I just want to acknowledge we are aware of the challenges associated with these other programs and we are working to resolve them. Thank you for the opportunity.

Clarifying Questions (continued)

DR. BATEMAN: Thank you.

So we'll now go back to clarifying questions for the sponsor. I'd ask everyone on the advisory committee, please just limit your questions to a single question, and if you have a second question, we'll come back around to you if we have adequate time.

So a question for the sponsor, Dr. Zacharoff?

DR. ZACHAROFF: Hi. This is Kevin Zacharoff from Stony Brook Medicine. My question, I'll limit it

to one question for the sponsor. Is there any data that the sponsor has with respect to administration of this medication after the patient has received prophylactic dose of ondansetron? Thank you.

MR. SCOTT: Yes, thank you for your question. If we could pull up the PONV-OINV slides.

Dr. Schachtel, can you speak to this?

DR. SCHACHTEL: Yes. Hi. The direct answer to your question is not that specific treatment to prevent postoperative nausea and vomiting, but we did do something else, which I think is analogous and answers your question nonetheless. What I did was measure nausea and vomiting before the administration of an opioid. These are patients who had non-opioid postoperative nausea and vomiting before they were exposed to an opioid. Let me show you what I mean.

If you look at the slide numbers BU-9, if you could pull it, this shows the pre-opioid -- or pre-hydrocodone in this case -- administration. You see in the 002 study, looking at the orange and purple group, you see the incidence of nausea. None of them had vomiting, by the way, before administration of an

opioid. Likewise, in the 003 study, both groups were pretty homogeneous in terms of having nausea before administration of an opioid.

The next slide, please, these are the remaining patients. These are the people who did not have any nausea before they were administered hydrocodone, and you can see on the left that the Norco-treated patients, there was an incidence of OINV over 3 to 4 hours at 30.8 percent compared to 8.6 percent among Hydexor-treated patients.

In the 003 study, where the treatment observation period was 48 hours inpatient, the incidence was 41.5 percent compared to 9.8 percent. Obviously, there are clear differences there of clinical importance in terms of reduction and a relative risk. The next slide answers your question, I think, better.

Could I have the next one, which is 11, BU-11? Very good. Now, here you see patients who had nausea and then were administered, under double-blind conditions, either the hydrocodone drugs or placebo. The left, you can see the difference of 32.7 percent

incidence of OINV versus 14, and of particular note on the right, you can see that the incidence of OINV actually increased among patients on Norco. It's 55.2, and it was 41.5 percent before. The difference from hydrocodone is 17.4, again, another significant relative risk reduction.

So I hope this helps. I think that's the genesis, or reason I should say, for your question, and I hope this answers it.

George, back to you.

MR. SCOTT: Thank you, Dr. Schachtel.

Also, Dr. Gan, if you could address this too, what you see in practice and in light. Then I know there was an open question regarding rehab facilities and discharge criteria, et cetera. If you could address that as well.

DR. GAN: Sure. To Dr. Zacharoff's question, in clinical practice, where we use ondansetron pretty routinely, obviously it's only typically effective about 30-40 percent of the time. So we do see a lot of patients develop nausea and vomiting following ondansetron prophylaxis.

In those situations, we will switch to a different antiemetic from a different class because data have shown that repeat of ondansetron while ondansetron is still on board, at least on the plasma level, has proven not to be effective. So we generally switch to a different class of antiemetics, and the choices are pretty limited.

As I mentioned earlier, the dopamine antagonists, histamine antagonists, and muscarinic antagonists, they all have side effects; in particular, sedation. Dopamine antagonists have QT prolongation side effects. So the question, that yes, we do see a lot of patients who failed ondansetron that we have to move to a different class of antiemetics. Hopefully, that answers your question.

Earlier I think there was a question about administering in the ambulatory surgery setting and the concern about sedation when these patients receive the combination drug. I would say to that is that we typically monitor patients until the patient is ready to be discharged, and that's including that they are not heavily sedated so that they can ambulate and they

can stand up by themselves. Hopefully that will reduce the risk of promethazine-related sedation.

Back to you, George. Hopefully that answers your question.

DR. BATEMAN: I'm going to move on to the next question just so we can get through as many of these as possible.

Dr. McCann?

(No response.)

DR. BATEMAN: Dr. McCann, you might be on mute.

DR. McCANN: Okay. Sorry. I'm off mute. I'm concerned about rehab facilities; for the most part very elderly people that break hips that end up in rehab facilities, and often they are part of skilled nursing facilities as well. Does the sponsor envision that this drug would be used in that particular setting?

MR. SCOTT: Thank you for your question. This is not indicated for skilled nursing facilities. And to the extent that they are attached to a certified medical facility, if they were discharged to a skilled

nursing facility, they would not be able to get administered Hydexor because of the limitation in the REMS.

I just want to clarify with respect to a REMS, we heard a lot about REMS programs. Most of the data that was presented was actually related to class-wide REMS, mostly to outpatient education programs. I think that the FDA has discussed Hydexor REMS is different than that, and here it's about controlling where the manufacturer is authorized to dispense Hydexor, which is only the certified medical healthcare facility, and certification of those facilities have the proper training and fall protocols in place with respect to Hydexor or specifically; and that all the physicians understand when they administer Hydexor, it is limited to the inpatient setting.

So if they were going to be discharged to anything other than that certified healthcare facility, which includes nursing facilities, which would not be certified, they could not be dispensed Hydexor.

Dr. Gan, clarify anything if there's anything else I'm missing in there.

DR. BATEMAN: Okay. I'd like to move on to the next question. Thank you for your response.

MR. SCOTT: Okay. Thank you.

DR. BATEMAN: Dr. Calis?

DR. CALIS: Hi. This is Karim Calis from the NIH. My question is actually with regards to the labeling, and the question has to do with the population. An opioid-naive patient who's never had surgery, kind of in the broader context of the types of patients that you've studied, my question really has to do with how do you implement or operationalize the very narrow indications for use and the limitations of use in a real-world clinical setting? I'm not sure how you operationalize that. Can you elaborate on that, please?

MR. SCOTT: Yes. Thank you.

Dr. Gan, can you speak to that, please?

DR. GAN: Sure. Typically, the scenario may be that the patient who comes to us with high risk for nausea and vomiting -- and there are some risk factors that increases the risk. For example, being female, you are at three times the risk for nausea and vomiting

after surgery. Interestingly, a non-smoker increases the risk. A previous history of nausea and vomiting following surgery also is a risk factor. And most importantly, the use of opioid is a significant risk factor.

These are what we call high-risk patients. In the postoperative setting, for these patients we typically give prophylactic antiemetics, usually combinations; for example, ondansetron and a combination with steroid such as dexamethasone is very widely used. There are effective. However, there are some patients who still unfortunately develop nausea and vomiting after surgery because of all of these risk factors. So in those contexts or those patients in the postoperative period, when they require an analgesic, again, we try to stay away from opioids and try to give non-opioid analgesics, but we know that sometimes they are not enough, so we need to give opioid analgesics.

We know that these patients develop nausea and vomiting because of the opioids, and therefore we would typically give an opioid together with an antiemetic. In this context, we may give promethazine by itself,

but unfortunately my hospital only has 25 milligrams, and we know that sedation is dose proportional. So the combination pill with hydrocodone and half the dose of promethazine 12.5 would not only address the pain but also hopefully reduce the risk for nausea and vomiting.

I think those are the scenarios I see potentially where this drug would fit. I hope I answered your question.

Back to you, George.

DR. BATEMAN: Great. Thank you.

MR. SCOTT: Thank you, Dr. Gan.

DR. BATEMAN: Dr. Sprintz?

DR. SPRINTZ: Hi. Thank you very much. My question is for Dr. Scott. It's related to May 19th of 2019. In your response to the FDA, you had stated that you were willing to limit the use to postoperative patients in which OINV may be a barrier to wound healing, and now when I look at your current proposal for your indications, you've removed that statement.

I'm wondering, why did you offer this more limited, restricted indication, but now coming back? And I noticed that that's happened a couple of times

previously where you offer something in discussions with them that's relatively limited, and then when you make your formal submission, it's a broader one, and I'm wondering why that happened this time. Thank you.

MR. SCOTT: Yes. Thank you for that question, and the FDA can speak on this as well. All of our proposals, actually, we were putting those forth. Essentially, when the FDA responded, we generally agreed with their proposals. We never actually pulled anything back; it was just we had proposals and what the FDA would agree to.

With respect to wound healing, we actually initially agreed with that language, and then after further revisions that we received, that was no longer in there, and we, just as a general basis, agreed with what the agency proposed. I don't know if the agency wants to address this as well, but that is the answer.

DR. BATEMAN: Okay. Thank you.

Dr. Nelson?

DR. NELSON: Thank you. It's Lewis Nelson from Rutgers. I want to go back to the question I had addressed to the FDA and back to the sponsor. They're

sort of two related questions, but one of them is really what qualifies as a medically-supervised facility. Dr. Wolfe had brought up dentist, and others have brought up those sorts of facilities.

Given even surgery centers don't typically have very highly active and highly functional pharmacies attached to them, it's a little unclear how these medications are going to be used in settings like that, which brings me to the question about if a patient is entitled, so to speak, to 15 tablets over 3 days, if those get pulled down for the patient, how do we assure that they don't get distributed to that patient when they leave?

I understand that this is well intended to say that the doctor or the nurse, or somebody will give that patient the pill. We do know that human nature is such that there are workarounds to this, and this is where the other REMS that we've talked about had failed, and even well-intended REMS. Things that have very high expectations still have failed in the past; maybe not always, but enough that this does become a bit of a concern. Thank you.

MR. SCOTT: Yes. That's to the sponsor, correct?

DR. BATEMAN: That's right.

MR. SCOTT: Okay. Thank you.

Thank you for that. Just to clarify, the patient is not entitled to 15 pills. What we have is a cap at 5 pills per day and a cap at treatment no more than 3 days, and that's just from a review of our safety studies. Hydexor is prescribed as an as-needed basis. As opposed to in our clinical trials where we had forced dosing for the first 24 or 48 hours and we woke up the patient to dose them for clinical purposes, in practice, if they're sleeping, they would just sleep.

So once there's a discharge, they can no longer be administered Hydexor. What would occur is when a physician feels it's appropriate to administer Hydexor, only one pill would be retrieved, and that one pill would be administered in front of the healthcare professional. And not until the physician feels that another pill is needed, according to the indication and label limitation, that another pill would be dispensed.

So there is no situation where the physician or the patient would have more than that one pill per dose available, and the certification process would work with the FDA, where the healthcare facilities would meet these requirements, and only if they actually have an inpatient facility in the healthcare setting. So typically this wouldn't be a dentist organization.

DR. NELSON: Thank you. But a surgical center, which was I think in the list of places that was originally discussed, would qualify because they don't typically have inpatient settings either.

MR. SCOTT: Correct. A surgical center could qualify but, again, in order to be certified, they would have to meet the same requirements that a Hydexor REMS requires. The dispense of Hydexor is limited on an as-needed basis; so typically, if you're going to be in the inpatient, after you get off of IV. And then after that, if you're going to go to oral medication, you may have less than 1 day left in your stay. If Hydexor is appropriate, then you would get that for that one needed dosage, and then upon discharge,

Hydexor would no longer be available to that patient.

DR. NELSON: Okay. Thank you.

DR. BATEMAN: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. This is a follow-up question for Dr. Gan, I believe. Could you please clarify which are the comparative benefits of giving the combination product versus giving the opioid? And then as needed, giving a non-sedative, antiemetic, and it doesn't work, giving the antiemetic as needed for the patient.

DR. GAN: Sure. I will be happy to respond to that. The options are either you give hydrocodone and in this case promethazine 12 and half milligram as a combination product, or the alternative is to give hydrocodone and antiemetics as a separate product. So if you would like to give promethazine, the oral dose of promethazine currently available in most hospitals is 25 milligrams.

Certainly, I checked with my pharmacy. That is the only dose that is available. We know that promethazine in a dose-related fashion increases sedation, and therefore one would want to give the

antiemetic at the least amount of dose that is effective. And the combination with hydrocodone and with promethazine, 12.5 milligrams in Hydexor will give you an antiemetic that has shown to be effective and at the same time reduce the risk of sedation at 12.5 milligrams rather than the separate pills that would be 25 milligrams. I hope that answers your question.

DR. HERNANDEZ-DIAZ: Yes. Thank you. Yes, that was my question.

DR. BATEMAN: Okay. Next question, Dr. Horrow.

DR. HORROW: Yes. This is Jay Horrow. I have a question for the sponsor. I'm very confused about the discussion that just transpired about surgicenters. Most people understand surgicenters to be facilities in which there are no inpatient capabilities. So are you saying that this drug can be given in surgicenters and it can only be given where there are inpatients? This seems to most of us to be contradictory statements. Could you please clarify for us?

MR. SCOTT: Yes. Thank you. This drug can

only be given where there's an inpatient center.

DR. HORROW: Thank you. That's all.

DR. BATEMAN: Okay. Dr. Mehta?

DR. MEHTA: Hi. Reema Mehta. This question is for the sponsor. I was wondering if you could also just expand upon what training will be included in the program to ensure that the settings understand their requirements within the program, as well as what monitoring you'll be doing from the perspective of the sponsor to ensure that the program requirements are being met, as well as that the program would function as intended.

Then lastly, should you identify non-compliant actors within the program, what is your plan for addressing those non-compliant stakeholders?

(No response.)

MR. SCOTT: Sorry. This is George Scott. I just lost connection. Can you guys hear me?

DR. BATEMAN: We can. Thank you.

MR. SCOTT: Okay. Yes. I believe the question was regarding our REMS program and how the sponsor would work within that to ensure compliance,

correct?

DR. MEHTA: It was on a couple of different levels. One, the training for those, what training is going to be made available and what does that training look like for those that are going to be certified under the program? Then the next level was how you as the sponsor will monitor the effectiveness of the program. Then third, what actions you would take as a result of non-compliance within the program.

MR. SCOTT: Yes. Thank you. I appreciate that. So as discussed, Hydexor would be subject to a REMS program that is specific to Hydexor, so not the classwide REMS. In fact, IR hydrocodone-containing products, oral medication and the inpatient is not subject to a REMS, but if Hydexor was provided instead of Norco, for example, Hydexor would have a REMS.

So there's a certification process that our manufacturer would only deliver Hydexor to certified wholesalers who are certified to only distribute Hydexor to certified healthcare facilities. Part of the certification for the healthcare facility is that the personnel would be trained specifically on Hydexor

and its potential side effects, and how to administer Hydexor, and also have a fall protocol on site for the risk of sedation or fall.

Through that certification process, we would have auditing and constant reports, including pharmacovigilance, which we proposed in the outpatient but now it's included in this REMS, where we would have all the patient's data entered, and we would consistently have a survey of all these things for compliance and regular audit. To the extent either one of wholesalers or healthcare facilities were doing anything inconsistent with the certification, we would report that an obviously terminate the distribution of Hydexor in those locations. I hope that addresses it.

DR. BATEMAN: Thank you.

A reminder for advisory committee members, please put your hand down once your question has been answered.

Dr. Meisel? We have about five minutes left for clarifying questions, and then we'll move on to the committee discussion.

Dr. Meisel?

DR. MEISEL: Thank you. Steve Meisel with Fairview in Minneapolis. If I understand the proposal, Hydexor would only be available for an inpatient or perhaps a same-day surgery type of environment. But then they go home, and people still need opioids after surgery for some period of time. So presuming this product works as described, they've been taking Hydexor, and they take whatever, 5, 6, 8, 10 tablets during their hospital stay, and then they go home with a prescription, and that prescription, of course, would not be Hydexor; it would be plain Norco, or Vicodin, or something else.

Have you assessed the risk that there would be breakthrough nausea and vomiting in that setting now that the preventive antiemetic has been withdrawn? Thank you.

MR. SCOTT: Thank you for your question. No. Originally, our original indication proposed did include the outpatient setting, but we are a limited inpatient setting here. So upon discharge, the physician would have to, as you stated, prescribe an alternative medication that would be not what Hydexor

is indicated for.

DR. MEISEL: So just to clarify, there would be a risk that has yet to be defined or assessed or quantified that there would be breakthrough nausea and vomiting that would become a surprise to both the physician and the patient at that point, right?

MR. SCOTT: Well, let me turn to Dr. Schachtel on this for clarification. I'm not sure if I can characterize it as a surprise per se because our clinical studies were created for the outpatient setting included. However, we've mitigated through our label and our REMS to restrict it to the inpatient setting. So consequently, if opioid-induced nausea and vomiting was continuing to occur in the outpatient setting, then yes, Hydexor, since it's not administered in the outpatient setting, opioid-induced nausea and vomiting could definitely come back to play.

But Dr. Schachtel?

DR. SCHACHTEL: As I understand your question, Steve, you're asking have we studied patients who stopped using Hydexor and what's their outcome and how to treat it? Is that the --

DR. MEISEL: Basically, I think you've got the gist of it because obviously this would be stopped after 2 or 3 days, and then they go on to presumably the same drug without the promethazine. Is there a risk of -- the fact that if this drug works, as you suggest it does, in suppressing opioid-induced nausea and vomiting, now you no longer have that suppressant;

A, would it manifest itself, and B, could it manifest itself worse than it otherwise would have because you might have a rebound?

DR. SCHACHTEL: Ah, now I understand. Well, I have its evidence, obviously, beyond 3 days. But on day 3, 4, and 5 in the 003 post-bunionectomy study, you could follow the course of patients on Hydexor, and as their need for pain relief diminished, obviously fewer people took Hydexor and took fewer doses per day.

So among that group, the question would be, well, they now don't have any Hydexor because they're not taking it; what happens to those people who aren't taking it? And the answer is the incidence of OINV does not increase, or rebound as you're defining it; I like the term.

So that's the only thing I can tell you, that in the people who stopped taking Hydexor after day 2 -- we can look on day 3, we can look on 4 and 5, and we've seen this, and it's been submitted in the package you have -- the incidence of OINV among patients who stopped using Hydexor did not increase.

Back to you, George.

MR. SCOTT: Thank you, Dr. Schachtel. I hope that addresses it.

DR. BATEMAN: Okay.

We're now going to proceed to the charge to the committee from Dr. Roca.

Charge to the Committee - Rigoberto Roca

DR. ROCA: Hi. This is Dr. Roca. As I put forth the charge to the committee, there are a few points I really would like for you to consider as you begin discussing the questions that we will put in front of you.

It is acknowledged that this is a fixed-dose combination product. I am sure that there are some among us who have opinions about the pros and cons of a fixed-dose combination product. You've heard some of

them during the questions. Similarly, there are bound to be opinions about the advantages of one antiemetic over another. Lastly, there are probably some thoughts as to where exactly this product would fit in the clinician's therapeutic armamentarium. How will it be used?

However, although these points are certainly important, the question to be put forth during today's advisory committee is not about those issues. As you've heard this morning, the efficacy of the product has not been in question. The characterization of a safety profile to the individual components of a combination product has been characterized, as has a safety profile when these components are combined.

The question we would like you to discuss is whether the proposed label and REMS have adequately addressed the concerns raised by the observed safety profile. To that end, we have only one question for you, and perhaps we can put it up on the screen. I don't have it handy. But if we don't have it, that's ok, too. It is a voting question, but as you know, in addition to the vote, we find your discussions and the

reasons for you voting the way you did extremely valuable.

There we go. Thank you. The question we'd like to ask you is on the screen, and I suspect that Dr. Bateman will probably read it to the committee. But those are the things I would like you to consider as you move forward in your discussion. And again, thank you. We'll look forward to hearing what you have to say. Thank you.

DR. BATEMAN: Dr. Roca, before you go, can I just clarify? Do you want us to discuss the question before we take the vote or should we move to voting and then discuss the rationale for our votes after the voting's completed.

DR. ROCA: Sure. From my perspective, I'm really interested in, once you vote, the rationale as to why you voted the way you did. If you feel that there's any need for additional discussion, I think that would be fine. However, if you're feeling that you have heard enough, and you've got enough clarification as you needed, and are ready to go ahead and vote, that will be fine as well.

Questions to the Committee and Discussion

DR. BATEMAN: Okay. So why don't we take about 10 or 15 minutes. I'll read the question, we can have some discussion, and then we'll move to the vote around 12:30.

The question to the committee -- and I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request to the panel.

The question is, based on the revised indication and the proposed Risk Evaluation and Mitigation Strategy, which restricts the intended population and duration of use for Hydexor significantly from the originally submitted application, have the safety concerns been adequately addressed through labeling/REMS?

That's the question that's been posed. We have a few minutes of discussion. Please remember, you can't state the way you're going to vote, but if you'd like to bring up issues based on the presentations that we've heard from the sponsor and from the FDA that are

relevant to our deliberations around this question, we can do that now.

Dr. Roca, you have your hand raised.

DR. ROCA: Just a quick comment. As long as you make sure you don't state how you're going to vote. You can certainly discuss it, but you should not say how you're going to vote until you actually vote.

DR. BATEMAN: Okay.

So we'll move relatively quickly to the voting, but if anyone wants to either ask a question about the way the voting question has been framed or has points that they want to make that should inform the deliberation around the question, please raise your hand.

Dr. Calis?

DR. CALIS: Hi. This is Karim Calis from the NIH. Just a point of clarification. I'm still unclear about what constitutes a medically-supervised healthcare setting. Are we talking about strictly inpatient hospital settings only or can you elaborate in terms of what the agreement is between the applicant and FDA in terms of that question? Thank you.

DR. BATEMAN: Let's direct that to the FDA. Dr. Roca or Dr. LaCivita?

(No response.)

DR. BATEMAN: We can't hear.

Dr. Roca, are you able to respond to that question?

DR. LaCIVITA: Hi. This is Cynthia LaCivita. I'm sorry.

DR. BATEMAN: Okay. Thank you.

DR. LaCIVITA: Can you hear me now? From the FDA.

DR. BATEMAN: We can.

DR. LaCIVITA: Okay. It's intended to mitigate the risk for the respiratory depression and also the excessive sedation. Healthcare settings that dispense Hydexor must be able to meet the conditions laid out in the REMS, which would be to manage acute overdose and have fall precautions and protocols in place. They would have to have an authorized representative that would oversee the training and the institutional policies and procedures in their site with regard to how many days of treatment these

patients can receive, the things laid out previously. We make sure that the settings can meet the requirements, but we don't spell out which settings specifically in the REMS at this point in time.

DR. BATEMAN: Okay. Thank you.

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I am struggling with the question. In the discussion, I was hoping that the practicing clinicians could give us their opinion. It seems to me like the risks and benefits should be compared to the opioids plus the antiemetic and not in a fixed dose.

I think this question has two components in my mind. One is the market, like why would anybody use that? But I understand that that's not part of what we are supposed to comment on. But I think that there is a safety component associated with it, of giving the fixed dose versus giving the opioid antiemetic as needed. The only benefit for this risk-benefit balance that I understood is that this way we can reduce the dose of promethazine.

So I think we have not discussed the potential

benefits and risks of this in the sense that for patients, maybe just giving a lower dose of antiemetic will give the same benefit and maybe lower the risk.

For abuse, something that maybe we have not discussed is that having an opioid without the nausea and vomiting may actually increase the likeability and potential for addiction for a larger number of patients. I don't know if that's something that we want to consider, so I would love for the practicing clinicians to comment on this.

DR. BATEMAN: Does anyone want to weigh in on Dr. Hernandez-Diaz's question?

Dr. Jowza?

DR. JOWZA: Hi. Did you say Dr. Jowza?

DR. BATEMAN: Yes.

DR. JOWZA: Hi. I'm Maryam Jowza from UNC in Chapel Hill. I just wanted to address Dr. Hernandez-Diaz's question. I personally, as a practicing clinician, don't see a very large scope for this medication in the inpatient setting. There are a lot of alternatives. I agree with you that with the fixed-dose combination, you might run into some

limitations with how you use it. Personally, promethazine is not the antiemetic first or second line that we usually use, although the purpose of this medicine I guess is for people who have a history of opioid-induced nausea and vomiting, and maybe you want to decrease the pill burden.

Something that I do, along with what you said, worry about is having a combination medicine with the hydrocodone and the promethazine, both CNS depressants. There are some reports -- and some patients like the combination effect of having the opioid along with another CNS depressant. Some of the antiemetic medications, which tend to be sedating, are one of those medicines that are used concomitantly with an opioid medicine to help -- I don't know if it's the euphoric, but just the unintended positive addictive effect of the opioid.

So I think that's definitely a case, but I don't think that's what we're addressing for the question for this advisory committee.

DR. HERNANDEZ-DIAZ: Yes. Thank you.

DR. BATEMAN: Okay. Dr. Ciccarone?

DR. CICCARONE: Hi. Dan Ciccarone, University of California San Francisco. Just to weigh in on a comment by Dr. Hernandez-Diaz, I thought a lot about the misuse-abuse potential of this drug. I do know promethazine is a likable drug. It does have street value, particularly in combination with things like codeine or other opioids.

I'm fairly compelled that the REMS here addresses it, limiting it to the inpatient setting and limiting it to 3 days of dosing, so I don't have a large concern of escape to the street and becoming the new drug. So I just wanted to weigh in a little bit on that.

DR. BATEMAN: Okay. Thank you.

Dr. McAuliffe?

DR. McAULIFFE: Yes. I'd like to address Dr. Hernandez-Diaz's question as well. Promethazine in my practice has not typically been used as a first-line medication for nausea. It's typically reserved perioperatively for rescue as an antiemetic. So I think that when I see the labeling as only when non-sedating alternatives are not effective, that sort

of fits in as a rescue antiemetic. So that would be perhaps limiting it to a particular population, although that was not very clear how that would be operationalized.

The risks that are addressed by the REMS I think are adequately addressed in terms of certified medically-supervised facilities. There is a question of a 23-hour or 24-hour surgicenter. As Dr. Sprintz said, a patient could be discharged, have a dose of this drug, and then go home and take an opioid on top of that and have some drowsiness. But even if they're inpatient and they're within that 24 hours, and they're in the hospital, the severe drowsiness bothers me somewhat.

The falls and respiratory depression associated with that is addressed in the REMS, but what is not is a level less than that, that severe drowsiness in patients who are in the postoperative phase will affect their ability to ambulate, will affect their ability to cough and deep breathe, and in that light would decrease their ability to fight off the postoperative pneumonias and decrease postoperative

clots.

So I think that the drowsiness and the somnolence associated with that, again, is real, and falls are the ultimate, but there are a lot of risks involved that are less severe than that, that I think need to be addressed as well.

DR. BATEMAN: Thank you. I'd just add to that. In the FDA briefing materials where they presented the pooled efficacy studies and the opioid induced symptoms, there was a 32 percent prevalence of confusion in the Hydexor-treated patients compared to just 23 percent in the Norco patients; so not only more drowsiness but a substantially higher prevalence of confusion.

Dr. Zaafran?

DR. ZAAFRAN: Yes. Thank you. Sherif Zaafran, anesthesiologist in Houston. I'd like to, actually, just a couple things, echo, number one, that promethazine is probably one of the last drugs that we even like to give in our practice for nausea after prophylaxis with others, in rescue with others also.

From the standpoint of how we manage patients

right now, where we're minimizing opioids and maximizing non-opioids, the way this is, even with the REMS protocol, is kind of limiting, really, essentially what you're doing by giving a higher dose of an opioid and a subtherapeutic dose of the non-opioid. But when you do have issues, whether it be pain or nausea, on this medication, you're kind of limited already as to what you can give, both non-opioids and opioids, or even an antiemetic.

So from all the standpoints, it just raises a little bit of concern as to how practical it would be to manage a patient with this drug. Thank you.

DR. BATEMAN: Okay. Dr. Calis?

(No response.)

DR. BATEMAN: You might be muted, Dr. Calis.

DR. CALIS: No, I'm sorry. I forgot to lower my hand. Sorry.

DR. BATEMAN: Okay. Dr. Horrow?

DR. HORROW: Yes. Jay Horrow from Bristol-Myers Squibb and also a practicing clinician for over 40 years, and I have found promethazine to be a valuable adjunct to be used when needed; that is when

other antiemetics have failed, and I believe that is how this is being promoted here in terms of the label.

The issue is not will this drug be used commonly and will there be great use for it? The issue is will it be a useful adjunct to the clinician in taking care of patients who persist with nausea and/or vomiting and need opioid medications? And I believe that it does, and that the proposed REMS and other labeling restrictions here go well beyond any concerns that have been raised in the past regarding the safety. Thank you.

DR. BATEMAN: Okay. We'll take just a couple more comments. And again, please focus your comments on things that should help inform the deliberation but not on the way you're going to vote or the specific question being asked.

Dr. Meisel?

DR. MEISEL: Thank you. Steve Meisel with Fairview in Minneapolis. I frankly think that the proposed REMS here doesn't address the concerns in an awful lot of ways. We talk about the fact that the elderly are problematic, so we're just going to limit

it to the hospitals and not nursing homes. Well, an awful lot of people who are elderly receive surgery in the hospitals and there's no dose or restrictions for the elderly, so that's one problem.

We say, well, there's a risk of falls when people get sedated, so we'll just do it in the hospitals. But I can tell you that when we put patients into falls risk, the first thing we do is take away added risks. We don't introduce new risks, which would be the case with Hydexor, adding yet another risk.

The suggestion that, well, we're going to limit it to patients who have a high risk of opioid-induced nausea and vomiting, I've yet to hear how one differentiates that other than just know it when they see it. But Dr. Gan suggested that anybody on an opioid is considered high risk, and therefore anybody post-op who receives an opioid would qualify for this drug.

A maximum of 5 doses per day, and then what happens when you need more? That hasn't been well-ironed out. I can tell you from a practical point

of view, perhaps only prescribed q4 hours PRN maximum of 5 doses per day, that is almost impossible to effectively administer, so people will get 6 doses per day, not by intent but just by the way these things sort of happen.

I think there are some good intents behind this in terms of language, but when you start to peel away the onion, I think those risks are quite there, quite profound, and could actually be higher than otherwise would be the case because there's a false sense of security. Thank you.

DR. BATEMAN: Thank you.

We'll take one more brief comment from Dr. Sprintz, and I'd remind all of the panelists, please place your phones on mute if you're not speaking.

Dr. Sprintz?

DR. SPRINTZ: Hi. This is Dr. Michael Sprintz. I wanted to address Dr. Hernandez-Diaz's comment as well. The thing that keeps coming to mind, I did acute pain for a number of years and anesthesia, and one of the things when we're talking about this

patient population, we're looking at a population of people that are inpatient, postoperative, which means the vast majority of them all have IVs in place.

So I'm still grappling with the idea of we're going to give a pill to someone who's got nausea and vomiting -- because a lot of times -- and I'm sure others have had -- I've had the problem of having the patient throw the pill up, and then it doesn't work anyway, and they have a useful IV in place. So for myself, the patient population we're talking about actually applying this for is exactly the population I wouldn't necessarily want to give a pill for.

Then another issue with that is the only area that I could see that being is, well, okay, the IV is out. Well, if the IV is out, that usually relates to the ambulatory surgery center where the patient's ready for discharge and then complains of nausea, but those are the people that we absolutely don't want to give it to because they're going home.

Those were some questions that I don't feel have been -- I'm just concerned about those things, let alone the addictive issue for the combination drug.

It's very popular. There is a street value for that, too. Thank you.

DR. BATEMAN: Okay. Thank you.

We'll now proceed with the voting question. Dr. Moon Hee Choi will provide instructions for the voting.

Dr. Choi?

Excuse me. We're going to go back to Dr. Roca for a comment before we move on to voting.

DR. ROCA: Yes. This is Dr. Roca. I was just going to comment that you should go on to the voting at this point, so you took care of my comment. Thank you.

DR. CHOI: Question 1 is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record, and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in

the breakout room. You should select the radio button that is the round, circular button in the window that corresponds to your vote: yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed.

Once all voting members have selected their vote, I will announce that the vote is closed. Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Next, the chairperson will go down the roster and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did if you want. However, you should also address any subparts of the voting question if any.

Are there any questions about the voting process before we begin?

(No response.)

DR. BATEMAN: Okay. If there are no questions about the process, then I'm going to read the question into the record.

Based on the revised indication and proposed Risk Evaluation and Mitigation Strategy, REMS, which restricts the intended population and duration of use for Hydexor significantly from the originally submitted application, have the safety concerns been adequately addressed through labeling/REMS? And if you voted no, please comment on what additional issues the applicant needs to address.

Are there any final clarifying questions, just clarifying questions about the wording of the question?

(No response.)

DR. BATEMAN: If not, we'll begin voting on question 1.

(Voting.)

DR. CHOI: Voting has closed and is now complete. The vote results are displayed. I'll read the vote totals into the record. The chairperson will go down the list and each voting member will state their name and their vote into the record. You can

also state the reason why you voted as you did if you want to. However, you should also address any subparts of the voting question if any.

For the record, we have 7 yes; 14 no; and zero abstentions.

DR. BATEMAN: Thank you. We'll now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification for your vote if you wish to. However, please remember to address any of the subparts of the question that correspond to your vote.

We'll start with Dr. Hincapie-Castillo.

DR. HINCAPIE-CASTILLO: Hi. This is Dr. Juan Hincapie-Castillo, and I voted no. I based my decision explicitly on the inclusion of labeling and the REMS. Whereas the REMS do impose a lot of limitations, I think the labeling is not very strong or clear enough. I think it's very hard still to identify those patients at high risk. I would suggest the sponsor look at maybe revising the labeling for patients with a history of opioid-induced nausea and vomiting. I'm very concerned about the safety issues in older adults since

these were very underrepresented in the studies. Thank you.

DR. BATEMAN: Okay. Thank you.

Dr. Jowza?

DR. JOWZA: Maryam Jowza. I voted yes. My main concerns were regarding oversedation and potential for risk for abuse. I do feel that with the risk mitigation strategies and restricting to inpatient use in a monitored facility, my concern has been met. I feel safe with it.

DR. BATEMAN: Thank you.

Dr. Porter?

DR. PORTER: Yes. This is Laura Porter. I voted no. I believe that when the patient is discharged after 3 days of being on the Hydexor, they will still have the issue of nausea and vomiting with opioids, so the Hydexor will only delay what is going to happen anyways. Also, I have a concern about the safety issues; particularly in the elderly, the risk of increased sedation and also the addiction potential. Thank you.

DR. BATEMAN: Dr. Zaafran?

DR. ZAAFRAN: Thank you. Sherif Zaafran. I voted no. My concerns are that even with the risk mitigation procedures, if a patient needs a rescue medication, that you're adding on to it the potential risk of even more sedation. The use of it in that kind of inpatient setting is really impractical, as you have the way the drug is combined in that matter and that fashion. And again, from the standpoint about discharge, you're kind of running into the problem of a patient still having these symptoms, yet having to deal with giving them medication separately. And for that, I voted no -- [inaudible - audio gap].

DR. BATEMAN: We've lost you at the end.

Dr. Zaafran, are you --

(No response.)

DR. BATEMAN: Okay. We'll come back to you so you can complete your comments.

Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff, Renaissance School of Medicine at Stony Brook University. I voted no. And just to clarify, I voted no specifically with respect to the question at hand

with respect to the REMS, not whether the drug be approved with the intended labeling.

I voted no for a variety of reasons, many of which have to do with the wording of the suggested REMS. Throughout the briefing documents and even the elements to assure safe use, I saw the words "administer, dispense, distribute" used interchangeably, when in actuality they all mean different things, and I didn't feel the REMS satisfactorily addressed purely administering the medication to someone. When I hear words like "dispense" I think about somebody being given medication to go home.

I don't necessarily consider the REMS to be significantly clear with respect to the limited use of this medication in terms of limited settings. I would have much more preferred the word "inpatient use" because I don't consider there to be such a thing as an inpatient in situations like ambulatory surgical centers, and I found the word "certified clinical settings" to be unclear. If it had been "hospital inpatient settings," that would have gone a long way

for me.

Then lastly, I voted no because while I agree basically with every comment Dr. Gan made today with respect to real-world use of this medication, I haven't seen anything presented with respect to real-world use of this particular medication given the circumstances we're talking about. Oral surgery, bunionectomy, and osteoarthritis flares are not likely situations where this medication would be used as the REMS specifies. Thank you.

DR. BATEMAN: Dr. Michna?

DR. MICHNA: Yes. Ed Michna. I voted yes as to the REMS issues. The utility of this drug is another issue that we weren't asked.

DR. BATEMAN: Thank you.

Dr. Hovinga?

DR. HOVINGA: Collin Hovinga. I voted yes. I focused largely on the REMS and the risk mitigation strategy imposed, not on efficacy or the standard of practice and where this lies. Given that, I voted yes.

DR. BATEMAN: Thank you.

Dr. Goudra?

DR. GOUDRA: Dr. Basavana Goudra from Penn Medicine. I voted no. One, there are plenty -- I wouldn't say plenty. There are certain antiemetics which are non-sedative, and given the variability in response, especially across age groups and patients with associated commodities, I don't think adding another sedative to opiates is a good thing.

Promethazine is certainly not the first-line antiemetic, and I don't prescribe it much, and I don't know when was the last time I prescribed it. Other than convenience, quote/unquote, "convenience" of combining these two, I don't see any good reason or purpose for this, and that's the reason I voted no. Thank you.

DR. BATEMAN: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted no. It was not easy because I do agree that the sponsor has really restricted intended population and duration and substantially modified the labeling and the REMS. The use proposed is above standards compared to other opioids. However, I still, probably 51 to 49, voted no because I think there are remaining safety

concerns that outweigh what I can see as huge benefits compared to given the opioids without [indiscernible] antiemetic.

DR. BATEMAN: Okay. Thank you.

Dr. Ciccarone?

DR. CICCARONE: Hi. Dan Ciccarone, UCSF. I voted yes. I believe that opioid-induced nausea and vomiting is a real clinical problem. I believe the company has addressed all the FDA and advisory committee concerns over four reviews. I agree with others that there's some clinical limitation here given the fixed-dose regimen, but that's left up to the clinicians. That's not for us to decide today.

The question for us is around have safety issues been addressed. I do think the REMS, which is specific to this product, appears to be adequate for population level safety concerns, for example, opioid misuse, as well as individual patient safety issues. So that's why I voted yes to this question. Thank you.

DR. BATEMAN: Thank you.

Dr. Sprintz?

DR. SPRINTZ: Hi. This is Dr. Michael

Sprintz, and I voted no. Based on the question being asked, I believe that the risks still outweigh any benefit of this combination product. I have a lot of concerns about the safety of this product in combination from an abuse and addiction potential. But regarding the actual voting question, I do not feel that the applicant has put together an effective plan for ensuring adherence to their suggestions for limiting distribution of the product, and that concerns me deeply about the risk for unintended consequences, including diversion, abuse, as well as accidental overdose.

The term "certified healthcare setting" also really concerns me because it can be interpreted in such an extremely broad way to cover a whole bunch of settings. I think Dr. Zacharoff had also commented on a much more specific inpatient hospital type definition is something that I would have felt more comfortable with.

Third, I know that a number of opioid REMS programs, while they all start with good intentions, oftentimes don't succeed in their goals and with some

severe unintended consequences, and I'm not confident that this REMS solution that was offered today would address the safety concerns listed. Thank you.

DR. BATEMAN: Dr. Arfken?

DR. ARFKEN: This is Cynthia Arfken. I voted no. I'm concerned about the safety in the elderly, and not enough information was provided for that. I'm also concerned about actually implementing the labeling and the REMS. The labeling has to do with the private insurance and other payers who decide whether they will pay for it. I found the labeling too vague. Thank you.

DR. BATEMAN: Dr. Calis?

DR. CALIS: Hi. This is Karim Calis, and I voted no, again, for really safety concerns. Both with regards to the REMS and the labeling, I think in terms of the REMS, I think the terminology should be much more explicit about what constitutes a medically-supervised healthcare setting. Certainly ambulatory surgical centers, to my mind, diverge from an inpatient setting. The stay there is limited to a few hours. There may be a temptation even to continue

a medication, perhaps mistakenly, with the thought of completing a 3-day course. I know that would be unintended but certainly possible.

I also really feel that in terms of -- I know Dr. Gan addressed who would be at high risk, female, et cetera, but I think, really, it's very difficult to implement and operationalize the indication for use, even in the context of the limitations of use as well.

How can you really implement what's severe enough to require an opioid; and only when non-sedating alternatives are not tolerated or ineffective; and what's high risk? Especially in opioid-naive patients, patients having surgery, looking at it in the context of the types of surgical procedures other than bunionectomies, and oral surgery, and things like that where you're dealing with a much more diverse patient population, I think the risks are still there, and I don't believe that labeling and the REMS really effectively address those. Thank you.

DR. BATEMAN: Thank you.

Dr. Shoben?

DR. SHOBEN: Hi. I'm Abby Shoben, and I voted

yes, basically on the strict interpretation of the question. The primary safety concerns in the previous submission, in my mind, were about the population level of risk to exposing people who wouldn't benefit, to the potential risk of having the extra sedation. And that risk has been well mitigated, I think, by doing this in an inpatient setting with appropriate precautions and a broader population public health risk of putting this drug out there that potentially has more abuse potential, and that's been well addressed by restricting the setting and restricting the number of days. Thank you.

DR. BATEMAN: Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. I voted yes. My initial safety concerns about use in older adults that I expressed in the 2018 advisory committee meeting has been adequately addressed through the labeling and REMS that was proposed for this meeting. Thank you.

DR. BATEMAN: Dr. McCann?

DR. McCANN: Hi. Mary Ellen McCann, Boston Children's Hospital. I voted yes. It was a very narrow decision. I basically read the question

literally, and I think the sponsor has responded to the concerns of the FDA and the meeting in 2018. I have concerns that the REMS won't be followed, but I don't think that we were asked to really discuss that or vote on that, so I voted yes. Thank you.

DR. BATEMAN: Thank you.

Dr. Habel?

DR. HABEL: Yes. This is Laurel Habel. I voted no, mostly because I think the REMS is still unclear on the settings where this could be given. I also thought there was a lack of clarity on how high-risk patients will be defined. That's all.

DR. BATEMAN: Okay. Thank you.

Brian Bateman, and I voted no. I remain concern about the risks of administering a CNS depressant alongside an opioid in the context of a substantial proportion of patients not likely to achieve benefit from the medication. We saw that 40 or 50 percent of the patients in the Norco group didn't have severe nausea, or moderate or severe nausea, and didn't require a rescue antiemetic.

So you're exposing a substantial number of

patients to this additional CNS depressant without a clear benefit, and while just administering the medication in a licensed healthcare facility mitigates some of the risk, it doesn't mitigate the risks entirely. Severe drowsiness and confusion have deleterious effects on patients. Even if it doesn't result in frank opioid overdose or falls, I think being severely drowsy, being confused, can compromise their ability to participate in their recovery, to breathe deeply, and do all of the things that we hope patients do in the postoperative period.

I think another concern is that elderly patients were underrepresented in the trials, and that's a group we would be concerned about, these effects of the CNS depressants being accentuated. I also worry about the fact that a large fraction of patients are on other CNS depressants, so benzodiazepine, Z-drugs, antipsychotics, which could interact with both the promethazine and the opioid to further increase the risk of adverse effects.

I think a way forward for me to feel comfortable with this, the sponsor would need to be

able to define the patients who are going to benefit from the treatment, so perhaps limiting the indication to patients who were experiencing nausea associated with the administration of opioids. But short of that, I think giving it in a prophylactic way is quite concerning.

Dr. Meisel?

DR. MEISEL: Hi. Steve Meisel M Health Fairview in Minneapolis. I also voted no. I agree with much of everything that Dr. Bateman just said, but in general, I think REMS programs are reasonably ineffective to drive changes in practice and improve clinical outcomes. I think that's been well described elsewhere, including in the public comment period.

The issue of the elderly is very important to me. The population that's received this drug has been small with the elderly, and they were underrepresented in that regard, and they are at high risk of adverse events from this sort of a product. By definition, these folks are at risk for falls, and as I think I mentioned earlier, one of the things that you do when you have patients who are at risk for falls is to take

away triggers for falls risk, and certainly promethazine is a trigger for a falls risk. If you give a drug that's going to be helpful in less than half the patients, that's certainly something that you would do on an automatic basis.

Again, the inability to describe what a high-risk patient is, is of high concern to me. Dr. Gan essentially said anybody on an opioid would be considered high risk, so that's basically carte blanche for everyone. I don't think the dosing limits are practical, 5 doses per day. There will be a great tendency, if the drug doesn't work, to give a tablet and a half, and then you're exposing somebody to even a higher dose of the promethazine. Some people may not even need 7 and a half milligrams of hydrocodone, and then you're giving them too much of that to start with.

Then finally, I have relatively little confidence that we could restrict the filtering of this product into the community. Patients go home after a day, day and a half, and they theoretically can get another half a dozen tablets or something. If there's a will, there's a way that that will get dispensed, and

find its way into a patient's pocket, and go home, so that's going to be a problem. And even when it doesn't, I think the risk of rebound nausea and vomiting hasn't been well described and could end up being an unintended problem.

So really on balance, I see little benefit, lots of risks, and those risks are not addressed by the REMS or the labeling. Thank you.

DR. BATEMAN: Thank you.

Dr. Nelson?

DR. NELSON: Yes. Hi. It's Lewis Nelson from Rutgers New Jersey Medical School, and I voted no. The REMS is an impressive attempt to address the risks, however, you know the expression, "Those who have failed to study history are doomed to repeat it." The broad limitation of the prior REMS, although seemingly appropriate at the time for their intended use, have to be heeded, for this opioid analgesic that has such limited clinical benefit over existing medications, to support the risk that it carries.

Bypassing the REMS, whether inadvertently through poor understanding or lacks enforcement, or

intentionally for philosophical or economic reasons, puts hydrocodone, the most widely abused and misused opioid, in a fairly high dose in what amounts to an anti abuse-deterrent formulation with both an anti- [indiscernible] and an additional psychoactive drug, onto the street, which raises very grave concerns for me.

The indications for use are fairly loose and very subjective, and the settings of use were left fairly unclear. So on this basis, I cannot support the approval of this combination drug. Thank you.

DR. BATEMAN: Thank you.

Dr. McAuliffe?

DR. McAULIFFE: Yes. Hi. I voted no, primarily for many of the reasons that have already been stated. The population I don't believe was adequately defined, and a great proportion, the majority of patients in fact, may be exposed to a drug that they will not receive benefit from in terms of antiemetic therapy.

They have adequately addressed the duration. I think that's good that they narrowed it down to

3 days and a maximum of 5 pills, which was I think an improvement. But in the labeling instructions, it said, "Discontinue as soon as the need for concomitant therapy is no longer necessary," which led me to wonder how would one even determine if an antiemetic is no longer necessary when it's administered empirically with each dose of hydrocodone? So I think that could be addressed as well, and I think I'll leave it at that. Thank you.

DR. BATEMAN: Thank you.

Dr. Horrow, you wanted to comment.

(No response.)

DR. BATEMAN: Dr. Horrow, did you have a comment?

DR. HORROW: Yes. Sorry. I was on mute. Just a congratulations to you, Dr. Bateman, on a well-conducted advisory committee, and an observation that your comments, as well as those of Drs. Calis, Zacharoff, and Habel, could provide a very positive way for the agency to move forward with improving the language and perhaps coming to a resolution here, but thank you.

DR. BATEMAN: Okay. Thank you.

Before we adjourn, are there any last comments from the FDA?

DR. ROCA: Hi. This is Dr. Roca. I just wanted to say thanks. We do appreciate your comments and your discussion, and we also appreciate you taking time, as I mentioned this morning, from your busy schedules.

Let me just see if there are any other comments from the rest of my team that they want me to pass on.

(No response.)

DR. ROCA: Okay, nothing other than saying thank you again for your assistance.

Back to you, Dr. Bateman.

Adjournment

DR. BATEMAN: Great.

Thank you, everyone, for your participation in the meeting. We will now adjourn today's meeting. Thank you very much.

(Whereupon, at 1:09 p.m., the meeting was adjourned.)