FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE (AADPAC) MEETING

Virtual Meeting

Wednesday, April 19, 2023

9:00 a.m. to 5:17 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Rhea Bhatt

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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(Chairperson)

Professor and Chair

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By courtesy, Professor of Epidemiology and

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

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

My name is Brian Bateman, and I'll be chairing this meeting. I'll now call the April 19, 2023 Anesthetic and Analgesic Drug Products Advisory Committee meeting to order. Rhea Bhatt is the designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

MS. BHATT: Good morning. My name is Rhea Bhatt, and I'm the acting designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

First we'll begin with the AADPAC members, starting with Dr. Bateman.

DR. BATEMAN: Good morning. Brian Bateman. I'm professor and chair of the Department of Anesthesiology, Perioperative and Pain medicine at Stanford University School of Medicine.

MS. BHATT: Thank you, Dr. Bateman.

Next, we have Dr. Bicket.

DR. BICKET: Good morning. My name is Mark Bicket. I'm an assistant professor and director of opioid and pain research at the University of Michigan Medical School in Arbor, Michigan.

MS. BHATT: Thank you, Dr. Bicker.

Next, Dr. Jowza.

DR. JOWZA: Good morning. My name is Maryam Jowza. I'm associate professor of anesthesiology and pain management at the University of North Carolina in Chapel Hill.

MS. BHATT: Thank you.

Next, we have Dr. McAuliffe.

DR. McAULIFFE: Good morning. I am Maura McAuliffe. I am professor emeritus at the College of Nursing at East Carolina University, and my expertise is perioperative anesthesia and

analgesia.

MS. BHATT: Thank you, Dr. McAuliffe.

Next, we have Dr. McCann.

DR. McCANN: Hi. My name is Mary Ellen McCann. I'm an anesthesiologist at Harvard Medical School and a senior associate in anesthesia at Boston Children's Hospital. Thank you. Bye.

MS. BHATT: Thank you.

Next, we have Dr. Ness.

DR. NESS: Hi. I'm Tim Ness. I'm a professor emeritus at the Department of Anesthesiology and Perioperative Medicine at the University of Alabama at Birmingham. I'm still an active practicing pain clinician and have research related to QST, as well as clinical trial design.

MS. BHATT: Thank you, Dr. Ness.

Next, we have Dr. Shoben.

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

MS. BHATT: Thank you.

Dr. Sprintz?

DR. SPRINTZ: Hi. I'm Michael Sprintz, and I am adjunct assistant professor, University of Texas at Houston, Department of Internal Med in the Division of Geriatrics and Palliative Medicine, and founder of the Sprintz Center for Pain and Recovery. My area of expertise is the intersection of chronic pain and addiction medicine.

MS. BHATT: Thank you, Dr. Sprintz.

Dr. Zaafran?

DR. ZAAFRAN: Good morning. Sherif Zaafran. I am the vice chair of the Clinical Governance Board of the US Anesthesia Partners, the Gulf Coast region, and I'm also the president of the Texas Medical Board.

MS. BHATT: Thank you, Dr. Zaafran.

Next, we'll move on to our industry representative, Dr. Horrow.

DR. HORROW: Good morning, everyone. I'm Jay Horrow. I'm senior director of Global Drug Development at Bristol Myers Squibb, and clinical professor of anesthesiology at the University of Pennsylvania.

MS. BHATT: Thank you, Dr. Horrow.

Next, we'll move on to our temporary voting members. First, we have Dr. Brittain.

DR. BRITTAIN: Hi. I'm Erica Brittain. I'm a statistician at the National Institute of Allergy and Infectious Diseases, NIH.

MS. BHATT: Thank you, Dr. Brittain.

And Dr. Joniak-Grant?

DR. JONIAK-GRANT: Hi. I am Dr. Elizabeth Joniak-Grant. I'm a patient representative. I represent the number of chronic pain conditions. I'm also a sociologist who works with the Injury Prevention Research Center at UNC Chapel Hill.

MS. BHATT: Thank you, Dr. Joniak-Grant.

Next, we'll move on to our FDA participants. First, we have Dr. Roca.

DR. ROCA: Good morning. I'm Dr. Roca. I am the division director of the Division of Anesthesiology, Addiction Medicine, and Pain Medicine.

MS. BHATT: Thank you, Dr. Roca.

Next, we have Dr. Liberatore.

CDR LIBERATORE: Hi. This is Commander Mark Liberatore. I'm the deputy director for safety for the Division of Anesthesiology, Addiction Medicine, and Pain Medicine.

MS. BHATT: Thank you.

Dr. Kilgore?

DR. KILGORE: Yes. Hi. Good morning. My name is Elizabeth Kilgore. I'm a medical officer in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine. Thank you.

MS. BHATT: Thank you.

And lastly, we have Dr. Shibuya.

DR. SHIBUYA: Good morning. My name is Rob Shibuya. I'm a clinical team leader in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine.

MS. BHATT: Thank you, Dr. Shibuya.

That concludes panel and FDA introductions. Back to you, Dr. Bateman.

DR. BATEMAN: Thank you.

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 the 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 forum of this meeting.

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

Rhea Bhatt will read the Conflict of

Interest Statement for the meeting.

Conflict of Interest Statement

MS. BHATT: The Food and Drug Administration is convening today's meeting of the Anesthetic and Analgesic Drug Products Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committees are special government employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee 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 that 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 this committee have been screened for potential financial conflicts of interests of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of

postmarketing requirement 3033-11, issued to application holders of NDAs for extended release and long-acting opioid analgesics to evaluate long-term efficacy of opioid analgesics and the risk of opioid-induced hyperalgesia. The discussion will focus on a clinical trial designed to address these objectives. This is a particular matters meeting during which specific matters related to the NDAs for extended release and long-acting opioid analgesics under PMR 3033-11 will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements they have made concerning the products that issue. With respect to FDA's invited industry representative, we would like to disclose that Dr. Jay Horrow is

participating in this meeting as the non-voting industry representative, acting on behalf of regulated industry. Dr. Horrow's role at this meeting is to represent industry in general and not any particular company. Dr. Horrow is employed by Bristol Myers Squibb.

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

DR. BATEMAN: We will now proceed with FDA introductory remarks from Dr. Roca.

FDA Opening Remarks - Rigoberto Roca

DR. ROCA: Good morning. Dr. Bateman, members of the committee, and invited guests. My name is Rigo Roca. I am the division director of

the Division of Anesthesiology, Addiction Medicine, and Pain Medicine, in the Office of Neuroscience. As was mentioned a few minutes ago, today we will be discussing a protocol design intended to address a postmarketing requirement, also known as a PMR, that was issued to NDA holders of extended-release, long-acting opioids. You'll hear us refer to them as E-R-L-As or ER/LAs, and this PMR was issued in 2013.

As you have read in the background materials prepared for this AC meeting, the purpose of a PMR is to assess the risk of opioid-induced hyperalgesia, following the long-term use of ER/LA opioids. The PMR studies are also intended to evaluate the long-term effect of opioid medications. You have read about the results of a first attempt to design and conduct a study to address the PMR and the outcome of that attempt, and you have read about the continued discussions over the years that have led us to today's meeting.

Although we feel that the design of the proposed protocol to be discussed has the potential

to achieve the stated goal, it is not a final protocol, and we are open to your thoughts, comments, suggestions, and recommendations regarding the protocol, both the overall design and details of the protocol.

Of note, some of you may be aware of the announcement last week that the agency issued a request for labeling updates to the prescribing information for immediate relief, IR, and extended relief long-acting opioid analgesics, which included a new warning about opioid-induced hyperalgesia. It is important to note that there is more to learn about OIH, and the protocol and the discussion may provide information that could result in additional updates to the prescriber information.

To that end, last week's announcement should not impact the relevance of the proposed protocol, and I would like the focus of today's discussion to be on the protocol and not the SLC that was issued last week.

In the next few minutes, I would like to

briefly review the agenda for today's meeting, and if possible, perhaps we can show it, and if not, I can speak to it as well.

After the presentation by the Opioid Marketing Requirement Consortium, which is also OPC, there will be a taped presentation by Dr. Farrar. After a break for lunch, Dr. Kilgore will present the FDA's perspective. Each of the presentations will have a short period of time for clarification questions after the presentation. Dr. Kilgore's presentation will be followed by the open public hearing. After the open public hearing, I will give the charge to the committee.

As you listen to the presentations, I would like you to keep in mind the topics for consideration that were presented in the background. These will be to consider, in general, the proposed protocol design and the potential advantages and disadvantages of the design, and we would very much welcome and are open to comments and discussions about other designs that could potentially address the question that we're trying

to answer, in particular about the long-term effectiveness of opioid medications in the treatment of chronic pain.

Lastly, we welcome comments directed at specific aspects of the protocol itself; for example, anything from the inclusion criteria; the choice of comparator; aspects that impact the maintenance of the blind; and proposed endpoints. We look forward to your discussions, and we thank you for taking time away from your busy schedule to assist us. Thank you.

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

For this reason, FDA encourages all participants, including the industry's non-employee presenters, to advise the committee of any financial relationships they may have with the

industry, such as consulting fees, travel expenses, honoraria, and interest in the industry, including equity interests and those based upon the outcome of this meeting.

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

We will now proceed with the Opioid PMR Consortium's presentation.

OPC Presentation - Charles Argoff

DR. ARGOFF: [In progress] -- the persistence of efficacy of an extended-release long-acting, or ER/LA, opioid, in the treatment of chronic non-cancer pain, and includes an assessment of opioid-induced hyperalgesia. The design has been submitted to FDA and is the focus of today's meeting.

Good morning. I'm Charles Argoff, a

neurologist and pain management specialist. I'm a professor of neurology at Albany Medical College, the director of the Comprehensive Pain Center, the director of the Pain Management Fellowship, and vice chair of the Department of Neurology at Albany Medical Center. I'm also the president-elect of the American Academy of Pain Medicine.

I've been treating patients with chronic pain for over 30 years, and I have led numerous research studies, authored and co-authored peer-reviewed publications, and edited and co-edited multiple pain management textbooks. I have been compensated for my time. I have no financial interest in the sponsor companies or the outcome of the meeting.

I'm study lead of the clinical trial under discussion today, Study 3033-11. In that role, I have been working with OPC, the Opioid Postmarketing Requirements Consortium, and other independent experts to help develop a protocol to meet FDA's requirements, which are to assess the long-term efficacy of extended-release long-acting

opioids and the risk of opioid-induced hyperalgesia.

After this introduction, I will present the design of Study 3033-11, a protocol designed in collaboration with FDA and external experts to meet the remaining postmarketing requirement for a clinical trial to assess the long-term efficacy of ER/LA opioids and the risk of opioid-induced hyperalgesia.

Dr. Nathaniel Katz will then provide the rationale for the study design, in particular, how it addresses some of the challenges of prior designs. Dr. Katz has conducted numerous clinical trials and helped design Study 3033-11. He has also been involved in developing the IMMPACT guidelines for the design of pain trials. IMMPACT is the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. This group was formed to aid in the development of trials for all analgesics, including non-opioid and opioid analgesics, given the complexity of pain studies.

One of the key secondary endpoints of the

trial is an evaluation of the risk of opioid-induced hyperalgesia, or OIH. Dr. Morton Angst is a leading expert in OIH and will provide a background on OIH and its assessment. Dr. Angst helped design the OIH portion of the protocol.

Dr. Sandra Comer is a professor of neurobiology in the Department of Psychiatry at Columbia University and director of the opioid laboratory in the Division on Substance Use Disorders at the New York State Psychiatric Institute at Columbia University Irving Medical Center. She will describe protocol considerations for Study 3033-11. I will then return to conclude the presentation and lead our team in responding to questions.

As summarized on this slide and described in detail in OPC's briefing document, FDA issued a series of postmarketing requirements, or PMRs, in 2013 to the manufacturers of ER/LA opioids. The Opioid Postmarketing Requirements Consortium, or OPC, was formed in October of 2013 to answer specific questions about the long-term efficacy of

ER/LA opioids and the risk of opioid-induced hyperalgesia.

OPC has completed 10 of these 11 studies already. The 10 completed studies were observational studies to assess the occurrence of misuse, abuse, addiction, overdose, and death associated with the use of ER/LA opioids. The remaining study required, under the PMR, is a clinical trial.

The design of Study 3033-11 to evaluate long-term efficacy of opioid analgesics and the risk of opioid-induced hyperalgesia is the subject of today's discussion. FDA issued the initial ER/LA PMRs in 2013. Over the next year, OPC worked with FDA and external experts to design the initial protocol for Study 2065-5, which was submitted to FDA in November of 2014.

Study 2065-5 was the first clinical trial OPC developed and the predecessor to Study 3033-11. FDA stated that the primary focus of Study 2065-5 should be to estimate the risk of OIH. OPC continued to develop the study design and submitted

the final protocol to the FDA in January of 2016. Later that year, in September 2016, the first participant for Study 2065-5 was screened. Sixteen months later, FDA and OPC agreed to terminate Study 2065-5 early, due to an inability to recruit a sufficient number of participants.

In June of 2018, OPC, in consultation with FDA and outside experts, developed a new trial design, Study 3033-11, and submitted it to FDA. In November 2019, after continued discussions with FDA and external experts, FDA shifted the primary focus of Study 3033-11 from assessing OIH to assessing the long-term efficacy of ER/LA opioids, with the assessment of OIH as a secondary endpoint.

In April 2020, FDA expressed concern with the parallel group design of the study and recommended that the study use an enriched enrollment randomized withdrawal, or EERW, design. In October 2020, OPC submitted a revised protocol synopsis incorporating FDA's recommended changes. Over the next 18 months, FDA and OPC continued to collaborate on various features of the study

design, including, for example, the choice of study drug and refinement of the OIH protocol.

In March 2022, after further discussions with FDA and external experts to develop the design, OPC submitted the current draft protocol for Study 3033-11. In June of 2022, FDA informed OPC of the agency's intention to hold this advisory committee meeting.

The clinical trial PMR focused on assessing the risk of OIH following the long-term use of high-dose ER/LA opioids for at least one year. This included an assessment of the risk relative to efficacy. The clinical trial designed to address the PMR has evolved. The first study designed to satisfy this requirement, Study 2065-5, had as its primary objective to better characterize how OIH may relate to suboptimal responses to opioid therapy.

This study was designed in collaboration with FDA and external experts. It was initiated, but was terminated prematurely. Study 2065-5 had a randomized withdrawal design, enrolling

participants who were already on ER/LA opioids. To be eligible to enroll, participants had to have been on around-the-clock immediate-release or extended-release opioids for at least one year. In addition, they must have been on around-the-clock ER/LA opioids for at least 3 months prior to study entry.

The study was designed to randomize 820 participants. The investigators and everyone involved learned that most potential participants indicated reluctance to enroll in a trial that required them to taper off the medication on which they were stabilized. Potential participants were also concerned about losing access to opioid analgesic medications after trial completion.

Despite the best efforts of the investigators and OPC, this study could not recruit an adequate number of participants, and OPC and FDA agreed it was reasonable to terminate the study. During the 16 months after study initiation, only 32 participants reached the randomized phase. Through further discussions with FDA, a new

protocol evolved.

FDA determined that the new study should have a primary objective focused on the persistence of efficacy. Study 3033-11 eventually took shape with a primary objective to evaluate the long-term efficacy of ER/LA opioids, including exploring potential predictors of response and non-response, while also assessing the risk of developing OIH.

This shift in focus, along with the lessons learned from Study 2065-5, led to a different design for Study 3033-11. A key factor limiting enrollment in Study 2065-5 was that participants who were already on ER/LA opioids feared they would lose access to their medications. The new Study 3033-11 protocol would enroll and evaluate participants who are either currently utilizing or recently utilized prescribed immediate-release opioids and were still experiencing pain severe enough to warrant consideration of treatment with an around-the-clock ER/LA opioid.

Study 3033-11 is designed as a placebo-controlled, enriched-enrollment, randomized

withdrawal study or EERW. There is an extended open-label titration and treatment period, together totaling 42 weeks prior to the randomized withdrawal phase. The EERW provides an opportunity to evaluate both effectiveness outcomes in the open-label titration phase and efficacy outcomes in the randomized double-blind, placebo-controlled phase. Prior EERW studies performed for the approval of ER/LA opioids included a similar titration period prior to the randomized phase and an extended 52-week open-label treatment period after the randomized phase.

The current study is designed to address the postmarketing requirement of showing the persistence of ER/LA opioid analgesic efficacy for a year or more by inverting that sequence, starting first with an extended 42-week open-label phase, followed by a randomized withdrawal phase. In this way, Study 3033-11 can more directly address the persistence of benefit in a randomized phase during the final 10 weeks of a year of treatment.

As clinicians who treat patients with

chronic pain, we strive to optimize the benefits of the treatment prescribed by titrating patients to an appropriate stable dose. In Study 3033-11, in a similar manner, participants are titrated to an appropriate dose during the titration phase, and can continue to refine their dose during the open-label treatment phase. After the open-label treatment phase, participants will be randomized to either continue on their medication at the same dose or be tapered off their medication during a 10-week evaluation period.

To help ensure continuity of care at the start of the study, all participants will be asked to provide contact information for a healthcare professional who can continue to manage them on an ER/LA opioid once they have been tapered off of study medication. The primary objective is to evaluate the persistence of analgesic efficacy of an ER/LA opioid in the double-blind phase in participants with defined chronic non-cancer pain who demonstrate initial analgesic efficacy and tolerability of their ER/LA opioid during the

open-label treatment phase.

Two secondary objectives are to explore the incidences of opioid-induced hyperalgesia and opioid tolerance. The 3033-11 protocol was submitted to FDA in March of 2022. Upon approval of the protocol, the plan is to conduct a feasibility analysis of the protocol before beginning the 52-week trial and to perform a pilot quantitative sensory testing, or QST study, to evaluate and refine this OIH assessment tool prior to its use in the trial.

As clinicians who care for people suffering from chronic pain, we always focus on individualizing care, and study findings can and help inform our decisions. This study has the potential to add to the evidence base regarding the efficacy of opioids.

The result of multiple placebo-controlled and open-label studies provide a substantial evidence base demonstrating the efficacy of opioids. A meta-analysis by Meske, et al. in 2018 analyzed 15 studies that were similar in their

design because they were all conducted to support product approval by FDA. The studies had a randomized, double-blind, placebo-controlled EERW design. The duration of these studies was approximately 3 months. The overall conclusion of this meta-analysis was that opioid treatment was associated with statistically significant improvements in pain intensity, as well as improvements in patient global impression of change.

Some of the most recent evidence of the long-term efficacy of ER/LA opioids was published January 2022 by Farrar, et al. Both Dr. Katz and I are among the co-authors of this paper. We analyzed data submitted to FDA for the approval of certain ER/LA opioids. Our analysis followed 3,192 participants from eight different studies, evaluating the long-term benefit during a prospective 12-month open-label period. We concluded there is a cohort of patients who have stable pain relief for up to one year.

The Meske meta-analysis of the EERW phases

of 15 different opioid studies included a total of 6,774 adults with chronic pain. Their meta-analysis found that these randomized, placebo-controlled trial of up to 3 months in duration each showed that opioids were associated with greater reductions in pain intensity than placebo. Specifically, they found that ER/LA opioids are effective in decreasing pain intensity for the diagnosis of chronic low back pain, diabetic peripheral neuropathy, and osteoarthritis.

The primary outcome of the Farrar analysis was to determine the proportion of participants at study end who had stable or reduced pain while receiving a stable or lower dose of an ER/LA opioid. The analysis found that of the 3,192 participants who were successfully titrated to an ER/LA opioid, 44.5 percent achieved the primary outcome after 12 months of treatment and had stable or reduced pain with stable or decreased dose of opioid; 22.6 percent of participants had stable or reduced pain but increased their opioid dose; 20.8 percent had increased pain while receiving a

stable or reduced dose; 9.5 percent of participants had both increased pain and increased opioid dose.

The authors concluded that evidence exists for a subpopulation of chronic pain patients who demonstrate continued benefit from open-label, ER/LA opioid treatment for up to 12 months.

The protocol design for Study 3033-11 will now be reviewed in detail. This protocol has been designed incorporating lessons learned following the early termination of Study 2065-5. The clinical trial PMR did not change, but the goals and design of the study has. This evolution reflects an ongoing collaboration between OPC and FDA, along with external experts, many of whom are with us here today. The resulting design reflects our ongoing efforts to develop a clinical study that meets the PMR and addresses the challenges encountered in Study 2065-5.

This study is designed to assess multiple outcomes related to opioid efficacy, effectiveness, safety, and tolerability. The primary objective of Study 3033-11 is to evaluate the persistence of

analgesic efficacy of an ER opioid in patients with chronic non-cancer pain who have been treated with IR opioids and have experienced a partial response, but who still experience pain severe enough to warrant consideration of an around-the-clock ER/LA opioid.

Beyond this primary objective, the study has a wide range of secondary objectives. These include the following: evaluating the incidence of opioid-induced hyperalgesia and opioid tolerance; the identification of potential predictors of opioid response; evaluations of physical function, anxiety, and depression; and evaluating the safety of the doses utilized.

Study 3033-11 has a placebo-controlled, double-blind EERW design. The study medication is oral ER morphine. The planned number of participants is 1,100 participants to enter the open-label titration phase with an expected retention rate of approximately 60 percent; 666 will enter the open-label treatment phase, yielding 400 participants to be randomized 1 to 1 to either

continue on ER morphine or to be gradually tapered off it to placebo.

The OIH substudy is expected to include 200 participants at designated sites. To assure that the study has an adequate number of participants, an interim analysis is planned after 50 percent of participants have completed the double-blind phase. This interim analysis will evaluate the conditional power of the trial based on this first cohort, and 200 additional participants may be added to cover any shortfall in power at that time.

Participants can discontinue the trial at any time and can also be discontinued at the discretion of the investigator and/or sponsor. All participants who receive at least one dose of study drug will be tapered off of study drug during the tapering and follow-up phase. Participants who do not attain adequate pain control can be discontinued from study medication. If the discontinuation occurs during the placebo-controlled randomized withdrawal phase, the

participant will be counted as a treatment failure. If this continuation occurs during the open-label phase, then that participant will not be eligible to enter the randomized phase.

Reasonable efforts will be made to ensure continuity of care. All participants, regardless of when they discontinue study medication, if deemed eligible to continue opioid therapy may do so under the care of a healthcare professional willing to continue opioid care.

In Study 2065-5, the eligible participants were already on a high dose of daily ER/LA opioids. We learned that this made recruitment more challenging than anticipated. The Study 3033-11 protocol aims to recruit a population of participants with chronic non-cancer pain who are not on ER/LA opioids and who have not experienced adequate pain control on IR opioids or with other treatment modalities. More specifically, the protocol requires that participants have received IR opioids for at least three consecutive months out of the 6 months prior to enrollment in the

trial. They will have had a partial response to IR opioids but not attain adequate pain control on IR opioids or other treatment modalities. This population of participants would be considered appropriate for treatment with ER/LA opioids.

At screening, participants will be asked to provide informed consent and will be evaluated for entry into the trial. To be eligible at screening, each participant must report a worst pain intensity score over the prior 7 days of at least 5 and not above 9, on a 0-to-10 numerical rating scale. Participants can be enrolled with a variety of different chronic pain conditions, including musculoskeletal, neuropathic, and post-cancer treatment pain.

Additionally, OPC has developed a novel tool to help identify appropriate participants for this trial, the Patient Treatment Response Questionnaire. The Patient Treatment Response Questionnaire was developed by OPC and independent experts to identify participants for whom alternative treatment options have been inadequate.

This extensive questionnaire provides an inventory of multiple treatments a participant may have experienced during their pain management journey. This questionnaire will help investigators to confirm the types of opioid and non-opioid treatments that potential participants have experienced prior to screening to help assure their suitability for enrollment in this study.

The questionnaire queries potential participants on their use of many specific therapies often used to treat chronic pain, including opioid and non-opioid analgesics; adjuvant therapy such as anticonvulsives; antidepressants; steroids; muscle relaxants topical treatments; and injections or pumps. It also addresses non-pharmacologic modalities, including physical therapy; behavioral therapy; surgical procedures; medical devices such as spinal stimulators; and other approaches. The questionnaire can be found in the appendix of the briefing document.

Use of cannabis, illicit drugs, and alcohol

is not allowed during the trial. This is consistent with the label for ER morphine, as well as common practice in pain management. In addition, many non-prescribed controlled substances, both opioid and non-opioid, are also prohibited. The Prescription Opioid Misuse and Abuse Questionnaire, or POMAQ, will be administered at screening and during the trial to identify behaviors related to misuse and abuse.

This is a validated tool that was developed as part of the OPC's 10 completed observational PMR studies. Quantitative urine drug testing will be performed at screening and throughout the trial. The testing will include illicit drugs, cannabis, non-prescribed controlled substances, and alcohol. A positive urine drug test during screening will result in exclusion from the trial. A positive test during the trial will be investigated per protocol and may result in participant discontinuation.

Contact information for participants' pain management and healthcare professionals will be

collected at screening. The consent process will allow participants' healthcare professionals to be informed of their participation in the trial. The investigator will communicate with the healthcare professionals using institutional review board approved letter templates at the time of trial entry and at end of trial. A participant profile document will be provided directly to their healthcare professionals at end of trial. This profile will include sufficient information to enable the healthcare professional to appropriately manage participants' pain.

All healthcare professionals' licenses and drug enforcement agency registrations will be verified. Unblinding information about the participants' treatment assignment will be provided to healthcare professionals to ensure appropriate continuity of care. Participants will be asked to not communicate their treatment assignment back to the study investigator or any research site personnel should they become aware of the assignment from their healthcare professional after

their last trial visit. For participants who do not have a healthcare professional, the investigator will make reasonable efforts to refer them to locally available medical and social services at the time of trial exit.

The primary endpoint of the 3033-11 study is the time to loss of efficacy during the double-blind phase. Loss of efficacy can occur in one of several ways: if a participant has a 30 percent or more increase in their recent worst pain intensity relative to baseline and is in at least moderate pain; or if a participant initiates a new therapy for their chronic pain; or if the study drug is discontinued for lack of efficacy.

Worst pain intensity, as assessed by a 0-to-10 numerical rating scale, has been extensively validated for many different analgesic treatments and has been used in prior clinical trials of ER/LA opioids for chronic pain. Choosing time to loss of efficacy as a primary endpoint simplifies handling of missing data for participants who discontinue, and provides more

statistical power than measuring change in Average pain intensity.

This study also includes a variety of secondary safety and exploratory endpoints. This is a partial list of additional endpoints that will evaluate various aspects of the efficacy, effectiveness, safety, and tolerability of the long-term use of ER morphine. The full list is included in OPC's briefing document. Of note, there are multiple secondary efficacy endpoints, assessing treatment failure, loss of efficacy, pain, function, and quality of life. Specific secondary outcomes aim to assess the incidence of OIH.

In this trial, OIH is defined as an increase in pain sensitivity from baseline as determined by QST, and no improvement in worst pain intensity while receiving at least as high a dose of opioid. A fibromyalgia tool, the Widespread Pain Index, also known as the WPI, will assess the spread of pain from the index site, an aspect of OIH.

Safety endpoints will assess sleep, anxiety,

symptoms of opioid withdrawal, and behaviors consistent with misuse or abuse. All study endpoints will also be assessed in a subpopulation of participants on doses 90 milligrams per day or higher. Many of these safety and efficacy assessments will be performed at multiple time points during the trial.

The primary endpoint of time to loss of efficacy is evaluated during the double-blind, randomized withdrawal phase. Many of the secondary efficacy endpoints are also assessed during the open-label treatment phase. Assessments of OIH will occur during both open-label phases, as well as the double-blind phase.

This is notable because assessing the incidence of OIH over 42 weeks of open-label treatment may provide important new information about the occurrence of this phenomenon in participants treated with ER/LA opioids for chronic pain. Also noteworthy is that the population exposed during the open-label phases will be larger than the population exposed during the randomized

withdrawal phase.

Safety endpoints will be evaluated throughout the trial. Opioid withdrawal will be assessed during the double-blind phase during which half of the randomized participants will be undergoing opioid taper to placebo. There is the potential for ER/LA opioids to affect the neuroendocrine system, including the hypothalamic-pituitary-adrenal axis. Because of this, the safety and well-being endpoints include assessments of endocrine and sexual function. The assessments of anxiety, depression, sleep, and suicidal ideation and behavior are also important in a chronic pain population.

One of the objectives of the protocol is to identify predictors of response and non-response to opioid treatment. The protocol includes a systematic approach to identify independent response modifiers using a logistic regression model. This model will include effects for treatment arm, predictors of interest, and interaction between the treatment arm and

predictors of interest. The predictors, to be examined, include a wide range of factors. They are listed on the right side of the slide, including demographics; medical and family history; the OIH assessment: anxiety, depression, pain catastrophizing, adverse events, and insomnia.

The Study 3033-11 study design is a 12-month randomized-controlled, double-blind trial to evaluate the efficacy of ER morphine in the treatment of chronic non-cancer pain. The current design may more closely resemble clinical practice because after the 6-week open-label titration phase, it includes 36 weeks of open-label treatment prior to the 10-week randomized withdrawal phase. In total, the trial allows for up to 52 weeks of treatment with an ER/LA opioid. This is significant because design allows us to assess the persistence of efficacy after 42 weeks of treatment.

Dose titration of the study drug occurs in the open-label titration phase. There are weekly study visits. Rescue medications are not permitted

during this phase. Participants already on an IR opioid will discontinue their prior treatment and begin treatment with ER morphine based on dose equivalency. Participants not receiving an IR opioid will initiate open-label ER morphine at a dose of 15 milligrams BID for a total daily dose of 30 milligrams.

The dose can be titrated to achieve efficacy when worst pain intensity score is 5 or more in the prior week and in the judgment of the investigator. The dose can be increased in increments of 30 milligrams per day, up to a maximum daily dose of 240 milligrams. During this phase and throughout the study, participants may taper off of study drug, and they will not be able to enter subsequent phases. Importantly, the duration of this phase is flexible to allow investigators to appropriately individualize the dose for the participants.

Participants who tolerate and respond to the study drug during the open-label titration phase can enter the open-label treatment phase. During this phase, participants will return to the clinic

every 4 weeks for ongoing trial assessments with remote contact between visits. Rescue medications are permitted during this phase and throughout the rest of the trial. The design allows for further refinement of the ER morphine dose during the extended treatment period. When necessary, participants will have their daily dose titrated to achieve efficacy up to a maximum of 240 milligrams; however, doses must be stable for the 7 days prior to randomization.

The extended open-label treatment period may provide informative data that more closely reflect clinical practice. The open-label period includes a titration phase of approximately 6 weeks, followed by a treatment phase of approximately 36 weeks. The initial titration period is flexible, which means that each participant may have longer or shorter titration in treatment phases. Either way, the two open-label phases will always total 42 weeks.

This is consistent with clinical practice. When we treat our patients with chronic pain who

require around-the-clock opioids to manage their pain, we regularly titrate to affect and monitor for safety. We do this carefully in ongoing dialogue with the patient to ensure that each patient is on the most appropriate dose.

To enter the randomized phase, the participant must meet the following requirements: a reduction in worst pain intensity of at least 30 percent compared to screening; and the participant and investigator must agree that the participant has had meaningful improvement; and the participant must tolerate ER morphine. Throughout the study, participants must otherwise continue to qualify for inclusion in the study.

Participants will then be randomized to two groups. One group will continue on a fixed dose of ER morphine and the other will be gradually tapered off ER morphine on to Placebo. The primary endpoint is an evaluation of time to loss of efficacy in these two treatment groups.

Participants randomized to the taper arm will be discontinued from study drug to placebo in

a structured and double-blind manner. The duration of the taper period is based on the stable dose of ER morphine at the time of randomization. The duration ranges from 1 week to the lowest dose of 30 milligrams per day, up to 8 weeks for the highest doses. Rescue medication will be used to manage pain and withdrawal symptoms during the randomized withdrawal phase.

At the completion of the 10-week randomized withdrawal phase, participants who are assigned to continue opioid therapy will then be tapered off of opioids. Additionally, those participants who discontinued prior to randomized phase will be tapered and followed after they discontinue.

The protocol specified rescue medications are acetaminophen up to 3000 milligrams daily and up to 30 milligrams daily of IR morphine. Rescue medication is allowed starting in the open-label treatment phase and throughout all the subsequent phases.

The incidence of OIH will be evaluated as a change in pain sensitivity. It will be assessed in

a substudy in the OIH population, which is planned to be 200 participants. The primary method of evaluation will use QST to determine changes in sensitivity to thermal pain. The WPI will be used to assess pain spread.

The current study design was developed over many years in consultation with FDA and independent experts. The primary objective is to evaluate the persistence of analgesic efficacy of ER morphine for chronic pain in those participants who demonstrate initial analgesic efficacy and tolerability. Two secondary objectives are the evaluation of the incidence of OIH and opioid tolerance. An additional objective is the identification of predictors of response to ER morphine. The study includes extensive assessment of all participants to better evaluate the long-term safety and efficacy of ER morphine. This design is intended to align with current clinical practice and to address the challenges encountered in Study 2065-5.

I'm honored to now introduce Dr. Nathaniel

Katz to provide the rationale for the design in which he played a critical role.

OPC Presentation - Nathaniel Katz

DR. KATZ: Good morning, everyone. My name is Nathaniel Katz. I'm a neurologist and a pain management specialist, and I've been focusing my attention on optimizing the design and conduct of clinical trials of pain treatments for about 20 years now. I have participated in the design of the study since the very beginning. I have been compensated for my time; however, I have no financial interest in the sponsor companies or in the outcome of this meeting.

I will now explain the rationale for the design of the present study, including its strength, its limitation, and alternatives. In my view, there is never a perfect clinical trial. There are different design options for different purposes, and all of them have their strengths and limitations.

For Study 3033-11, we had to balance the FDA's role for the fulfillment of the clinical

trial objectives against the challenges we encountered previously with recruitment and retention in Study 2065-5. The primary objective of this trial is to assess the persistence of efficacy of ER/LA opioids for at least a year of treatment. Secondary objectives include assessment of the risk of OIH and predictors of response and non-response. However, to overcome recruitment challenges, participation must be viewed favorably by both investigators and participants.

To some extent, these goals are at odds because the longer the duration of the study and the more endpoints it assesses, the higher the burden on both investigators and participants. So the question becomes how to best balance achieving the scientific objectives of the study and also successfully executing the study?

Since you're being asked to consider the strengths and limitations of the enriched enrollment randomized withdrawal, or EERW, design, compared to the more conventional and widely understood non-enriched prospective parallel

treatment design, I will begin by introducing the rationale for the EERW design, which is illustrated on the left of this slide and a conventional prospective treatment design on the right.

The EERW design, which is also called the randomized discontinuation design, was not originally developed for pain studies. It was developed in other therapeutic areas, such as hypertension, depression, and oncology. The reason it was developed was to determine whether participants who have been on treatment for long periods of time were really still responding to the medication or could have been doing just as well on a placebo.

The design was introduced to overcome the impracticality of studying de novo participants for long periods of time, prospectively, especially with long placebo exposure periods, which is why it was introduced for the present study. Instead, the EERW design engages participants who have already been on treatment for a long period of time, which of course is a subset of the broader population and

is not representative of the broader population. In effect, the open-label phase of the EERW design is very similar to clinical practice and gives clinicians a sense of how patients will do on open-label treatment, then the placebo-controlled phase ensures that treatment is still working better than placebo, so you get both effectiveness and efficacy in the same study, if you will.

It is important to realize that the EERW design and the non-enriched prospective treatment design are asking two different questions. The EERW design is asking the question of whether a medication that has been used for a long time is still effective, which we have been calling persistence of efficacy. The prospective treatment design is asking the question of whether a medication that is newly started is better than a placebo. For that reason, the results of these two kinds of studies cannot be directly compared.

Now let's look at these designs in more detail. The main differences between the two designs are as follows. First, as I said earlier,

the populations are different. The EERW design enrolls participants who have either already been on treatment for a period of time or are put on treatment for a period of time before they're randomized; so this design selects participants who at least are tolerating the medication and seem to be benefiting.

On the other hand, the prospective treatment design generally studies a broad population whose reaction to the medication has not been observed yet. Participants in the EERW design will have low pain scores when they're randomized since they're already on treatment, whereas participants in the prospective treatment design will have high pain scores since they're not on treatment.

Secondly, in the EERW design, efficacy is tested based on what happens when you take the treatment away. Efficacy is considered demonstrated if participants do worse when you take their treatment away and give them a placebo compared to if you continue treatment. In the prospective treatment design, efficacy is tested

based on what happens when you give treatment compared to placebo.

Thirdly, the endpoints may be different. In the EERW design, the measure of efficacy is often a time to loss of the original therapeutic response, although you can also measure differences in pain intensity or other measures at the end of the randomized observation period. In the conventional design, you always measure differences in clinical status between groups at the end of the treatment period.

Now let's discuss why we propose the time to loss of efficacy endpoint as the primary endpoint in this trial. This endpoint has been very commonly used in EERW studies across therapeutic areas. It was originally developed because were a participant to develop severe symptom recurrence after randomization, they could drop out of the study and get whatever clinical treatment they needed, and the primary endpoint would not be compromised. Of course, we still compare the groups at the end of the study, but those

comparisons can be compromised by extensive missing data.

I published a paper a few years ago looking at the statistical power of time-to-event endpoints versus conventional group mean differences in EERW studies of opioids, and it also turns out that the time-to-event endpoints tend to be more statistically efficient, which means you can decrease the number of participants needed in your study compared to the conventional endpoint.

The main disadvantage of the time-to-event endpoint is that they're hard to interpret. What is the difference in time to loss of efficacy of 5 days mean or 10 days? This issue was addressed by still measuring all the usual endpoints as secondary endpoints, such as group mean difference in pain intensity, proportion of responders, et cetera, so that all the usual data are still there for interpretation. It's also worth adding that the clinical interpretation of any endpoint can be subject to debate.

All of these scientific refinements become

moot unless participants are willing to enroll and continue to participate in the study. We learned this lesson the hard way in the previous study. I think the bottom line with respect to these two study design options is that participants will simply not commit to a year of placebo in this day and age. For that reason, to us, the prospective treatment design did not appear feasible. Furthermore, even if you could enroll sufficient participants, only about half of participants on active treatment will still be in the study in a year, and probably even fewer on placebo. This creates a significant missing data problem, which could compromise the validity of any scientific conclusions from such a study.

In the EERW study, it will still be a challenge to recruit participants; however, in the collective experience of those of us who do these studies, it's much easier to recruit participants for an EERW study because the patients will be on open-label medication for most of the duration of the study. While there certainly will be dropouts

after randomization, most of the dropouts count towards the primary endpoint, and therefore don't compromise its validity.

After randomization in an EERW design, half of the participants taper to placebo. This creates several different types of concerns. From a scientific standpoint, the main concern is that, in theory, tapering someone off opioids can cause the very familiar acute opioid abstinence syndrome, one of the symptoms of which is worsening pain. So you could say that worsening of pain in a patient in the placebo group is not because the opioid had been effective for them, but because you've now precipitated opioid withdrawal.

In practice, we've done dozens of EERW opioid studies with relatively fast papers and very close monitoring for opioid withdrawal, and measurable opioid withdrawal is only rarely seen. In this study, the proposed tapering period is actually significantly longer in past studies, and we will still monitor closely for opioid withdrawal to ensure that any pain increases in the placebo

group are not due to a subtle opioid abstinence syndrome.

In this slide, I've tried to summarize the main strengths and weaknesses of the two designs. While each of these factors could be discussed and debated at great lengths, I think the bottom line is that the prospective treatment design is just not feasible. Participants will be very reluctant to enroll, and if they do, past research suggests that the majority will not remain until the end.

The EERW design is more feasible. It does have some important limitations, particularly around the interpretation of our proposed primary endpoint, the theoretical potential for confounding by opioid withdrawal, and perhaps most importantly, interpreting and communicating the results. However, these concerns can be mitigated in the ways that I've discussed.

Another important issue regardless of design is how many drugs to study. Study 2065-5, the one that was terminated early due to recruitment failure, assessed two different opioids, ER

morphine and ER oxycodone. This proved extremely burdensome to all concerned. This motivated OPC to propose assessment of a single representative ER/LA opioid in the 3033-11 protocol.

ER morphine was proposed on the basis that morphine is the original prototype opioid and is widely used in U.S. clinical practice. The drawback of this approach is that generalizing the results of this study to other opioid molecules, which may differ from morphine, will require some conjecture, although studying two opioids still does not solve this problem.

You might be wondering why we think the currently proposed study can be recruited when the past study, which is also an EERW, could not be recruited. There are some important differences in the currently proposed study specifically to address this issue. In the past study, participants were already on an ER/LA opioid and were being asked to accept a 50-50 chance of losing that opioid for 6 months after a short period of open-label treatment. That was not appealing, to

say the least.

In the current study, participants with inadequate pain relief on IR opioids are being asked to enroll for almost a year of access to open-label ER/LA opioid treatment, followed by a relatively short time during which they might taper to placebo with access to opioid rescue medication. We believe that this will be more appealing to potential participants.

In summary, Study 3033-11 is designed to fulfill the clinical trial objective of assessing the persistence of efficacy through 52 weeks of treatment. The first 42 weeks of open-label treatment will assess tolerability and effectiveness over an extended run-in period that is much longer than that of previous opioid EERW studies and similar to clinical practice.

The EERW design enables the assessment that the persistence of efficacy in a cohort of participants would tolerate and respond to long-term treatment with an ER/LA opioid. The 10-week randomized withdrawal period minimizes the

period of potential placebo treatment, which may make trial participation more appealing than the 24-week randomized withdrawal period of the prior 2065-5 trial. In addition, it's easier to recruit patients into a clinical trial that have inadequate pain control and are being offered a treatment for it versus patients with adequate pain control or being offered the opportunity to lose access to that treatment.

In summary, there are advantages and disadvantages to different design options for this study. On balance, the EERW design appears to us to offer the best opportunity to accomplish the study objectives that have been set forth. Dr. Martin Angst designed the Opioid-Induced Hyperalgesia Substudy, which he will describe now.

OPC Presentation - Martin Angst

DR. ANGST: Good morning. I'm Dr. Martin Angst. I'm professor of anesthesiology, perioperative, and pain medicine, and I am the department vice chair for Strategy and Initiatives at the Stanford School of Medicine. I have been

compensated for my time. I do not have any financial interest in the sponsor companies or the outcome of the meeting.

I founded the Human Experimental Pain Laboratory at Stanford in 1996. We use pharmacometric and psychophysical principles, along with quantitative sensory testing, or QST, a key tool to reliably assess pain and analgesic efficacy in a variety of drug classes. Experimental pain models included models of acute pain such as thermal, electrical, and mechanical pain, as well as inflammatory models.

A major emphasis of the lab was studying opioid pharmacology, including the heritability of beneficial and adverse opioid effects such as opioid-induced hyperalgesia. We have published extensively on OIH. Our 2003 publication was the first to show a causal link between opioid exposure and post-exposure hyperalgesia. Our systematic qualitative review of OIH in anesthesiology in 2006 has become a landmark publication of the subject that has been cited over 1400 times.

My colleagues and I have published additional reviews, written textbook chapters, and have spoken on OIH many times at international congressional meetings. We have found that thermal pain QST is a reliable, feasible, and scalable approach suitable for multicenter studies. It has properties that allow for a stimulation algorithm that is, in my opinion, best suited to detect OIH. This has been the basis of the approach we used in Study 3033-11. I led the development of the OIH substudy for the protocol, which I will describe in more detail, discussing the available data on OIH.

Opioid-induced hyperalgesia has been described as a state of nociceptive sensitization caused by the exposure to opioids. The condition is characterized as a paradoxical response whereby an individual receiving opioids could actually become more sensitive to pain. Clinically, OIH is characterized by a patient receiving the same ongoing opioid dose and experiencing one or more of three major symptoms: an increase in pain intensity over time in the absence of progression

of the underlying disease; the spread of pain beyond the original site; and pain evoked by typically non-painful stimuli such as touch.

OIH has been reported as a clinical phenomenon in the literature, but the best evidence for OIH coming from the perioperative context and in preclinical models. OIH as a construct is understood. What's not understood is how to measure and/or diagnose the chronic pain patient population. At this point, there is no wide accepted operational definition of OIH, and there is no validated methods to measure or diagnose it in these patients.

OIH is clinically significant in the perioperative setting. Physicians observed increases in pain sensitivity associated with higher doses of opioids during surgery. This observation was thoroughly assessed, and multiple published reports demonstrated a clear correlation with the occurrence of OIH and the use of high-dose opioids during surgery. For example, a meta-analysis of 37 studies and a total of 1,494

patients found higher intra-operative remifentanil doses are associated with increased post-surgical acute pain. So we do know something about OIH pain, the perioperative setting, but that doesn't translate into knowledge of OIH in the management of chronic pain.

Surveys of health clinicians who manage chronic pain indicate that most practitioners do not often encounter patients with apparent OIH. Even with all the caveats about choice, we can infer that the incidence may be low, and Canadian pain clinicians found that based on the number of patients seen by these clinicians, the reported prevalence of OIH among patients with chronic pain was low. Similarly, another survey of opioid prescribers found that most believed that OIH was relatively uncommon in their clinical experience.

There is no established validated and widely accepted method to assess OIH in chronic pain patients. The most promising approach to changes in pain sensitivity related to OIH is the use of QST. QST is a laboratory technique to assess pain

sensitivity and response to noxious stimuli applied at a controlled intensity. While many consider QST to be the standard to evaluate OIH in pain patients receiving opioids, it has not been validated for this use in chronic pain patients. A systematic review found that the evidence of QST and OIH suggests that measures of heat pain sensitivity are the most promising approach. Based on these findings, QST is included in Study 3033-11.

While the initial clinical presentation of OIH and tolerance may be similar that both present increased pain at the same opioid dose, the underlying neuroadaptive mechanisms are quite different. Intolerance to continued exposure to opioids at the mu receptor results in a dampening or muting of the response to the opioid, as a result, the higher dose of opioid is required to overcome this muted response and achieve a similar analgesic effect, shown as a right shift of the dose-response curve on the tolerance graph. In contrast, OIH is an increase in pain sensitivity that we can conceptualize a down-shift of the

dose-response curve shown on the OIH graph. As opioids cause this down-shift, increasing the dose may actually worsen pain.

Increased pain sensitivity as measured with QST is a critical element of the definition of OIH in Study 3033-11. The incidence of OIH will be measured in multiple phases of the trial. OIH is defined as worst pain intensity being the same or higher compared to screening, mild on an equivalent or higher dose of opioid, and increased pain sensitivity as evidenced by QST.

In contrast, tolerance is defined as worst pain intensity being the same or higher compared to screening without an increase in pain sensitivity. So OIH and tolerance are different phenomena, and both will be systematically evaluated in Study 3033-11. Importantly, these endpoints will be evaluated at the end of the study because data from the entire study population are required to define the QST metrics indicative of OIH.

The trial protocol assesses all three clinical characteristics associated with OIH in

patients with chronic pain. Increases in worst pain intensity will be assessed with a numerical rating scale. The spread of pain from the index site will be assessed using the Widespread Pain Index of the fibromyalgia scale. And finally, increases in heat pain sensitivity will be assessed by QST.

Changes in worst pain intensity will be assessed throughout the open-label and double-blind phases of the trial. These will be used on a per patient basis to determine changes over time. Pain spread will be assessed in the open-label treatment phase and the double-blind phase. Changes in pain sensitivity will be assessed starting in the screening phase. QST assessments will be performed in a subset of participants from selected trial sites that are trained to perform QST. One advantage of the trial design is that it affords ample opportunities to assess OIH by QST that are not limited to the double-blind phase, including the 42 weeks of open-label treatment.

Protocol has been designed to capture QST

assessments in all patients in the OIH population, irrespective of the phase of the trial. The QST sessions will consist of a familiarization training phase, followed by an assessment phase. Participants will be trained and tested for satisfactory QTC performance at baseline to qualify for inclusion into the OIH population.

Between sessions, variability data will be inferred from two assessments performed at screening. This will allow construction of the distribution-based criterion to infer the presence or absence of OIH. Standardized language will be used for instructing participants and performing QST assessments. All QST operators will be trained and remotely supervised at the beginning of the trial and intermittently during the trial to assure strict adherence to the QST protocol. We plan to review the utility and feasibility of the QTC algorithm after testing 20 participants.

OIH is a much discussed phenomenon, but we have quite limited data on it in the chronic pain population. One challenge is that while OIH is

defined as a concept, there is not a validated or widely recognized approach to measure and diagnose it in individuals with chronic pain. Changes in heat pain sensitivity are viewed as the most promising approach to quantify OIH, however, this approach has not yet been validated in this population.

The 3033-11 study protocol is designed to assess the three cardinal symptoms associated with OIH. Changes in pain intensity will be assessed by worst pain intensity, pain spread using the Widespread Pain Index of the fibromyalgia scale, and changes in pain sensitivity with QST. The QST assessments will be limited to a subpopulation of participants due to the operational and practical challenges. There are important unanswered questions about OIH in individuals receiving opioids for chronic pain. The 3033-11 trial protocol has the potential to meaningfully add to our understanding of the incidence, magnitude, clinical presentation, and assessment of OIH in these patients.

Dr. Sandra Comer will now discuss protocol considerations.

OPC Presentation - Sandra Comer

DR. COMER: Thank you, Dr. Angst, and good morning, everyone. I'm Sandra Comer, professor of neurobiology in the Department of Psychiatry at Columbia University. My research focuses on the pharmacology of opioids and the development of medications for treating opioid-use disorder and opioid overdose. I'm director of the Opioid Research Laboratory in the Division on Substance Use Disorders. I've also served as the president of the College on Problems of Drug Dependence and currently serve as the public policy officer for CPDD. I have been compensated for my time, but I do not have financial interest in any of the sponsor companies or in the outcome of the meeting. I regularly develop and evaluate protocols involving opioid products and the patients who receive them.

Study 3033-11 may have implications for both clinical practice and the lives of individual

patients with chronic pain, which underscores the importance of designing a scientifically and operationally robust protocol. Currently, there is level 1 evidence supporting the efficacy of ER/LA opioids through 12 weeks; that is, there are multiple double-blind, randomized, placebo-controlled trials that have been presented in a systematic review and meta-analysis as reflected in Meske, et al., 2018.

The individual studies included in Meske's review have all been published in respected peer-reviewed medical journals, so the evidence supporting the efficacy of ER/LA opioids has withstood extensive scrutiny and is well established. As yet, there have been no randomized, double-blind, placebo-controlled trials demonstrating efficacy for 52 weeks.

While a single trial is not as compelling as multiple trials subjected to a systematic review, the single trial can provide level 2 evidence. Study 3033-11 would be the first trial to provide such evidence. Its unique design offers the

opportunity to assess the persistence of efficacy in the final 10 weeks of 52 weeks of treatment.

There is, however, level 3 evidence of effectiveness of ER/LA opioids through 52 weeks. The Farrar, et al., 2022 publication analyzes multiple observational cohort studies. These are open-label studies following participants for up to one year, demonstrating that there is a cohort of participants who attain pain control on a stable dose. These data have been published in this review, and they were also subjected to further scrutiny in that all the data come from studies submitted to FDA and supportive approved products.

Now, we are considering the first protocol designed to provide level 2 evidence of the persistence of efficacy through 52 weeks. To accomplish this, this study has a novel design. The goal of this novel study design is to contribute new placebo-controlled data on long-term efficacy of ER/LA opioids with the potential to show a persistence of benefit out to one year. The results could contribute to the evidence base to

support the individualization of care for chronic pain, but a single trial would need to be interpreted with caution in the absence of replication. This is especially true here, where the interpretation of a single trial could potentially negatively impact patient care.

This protocol has an extended run-in period, which includes the 6-week, open-label titration phase and a 36-week open-label treatment phase. This is designed to identify a cohort of participants who are responsive to and can tolerate an ER/LA opioid. The typical run-in period is 3-to-5 weeks in mostly EERW studies of new opioid pain medications. For this study, it's 42 weeks, which is 10 times the duration of the typical opioid study run-in period. The extended run-in period enables the assessment of the persistence of benefit during the final 10 weeks of a year of treatment and also may have implications for the interpretation of the study results.

In all studies, there is a risk of type 2 error, which in the current study would be failing

to detect a long-term benefit of ER/LA opioids when it does, in fact, exist. There is no precedent for the sample size calculation. In particular, the rate of attrition during the 42-week run-in may limit the power to detect a signal of benefit if not enough participants reach the randomized phase.

The novel design and the extended duration of the run-in period could increase the risk of failing to detect a signal of benefit, particularly if it selects for a randomized cohort who are less likely to report adverse events, including increases in pain and withdrawal symptoms. If that happens, participants in the placebo arm may not report increased pain and withdrawal symptoms, which could confound the results. A false negative result that incorrectly points to a lack of efficacy could have broader consequences for the treatment of patients with severe chronic, non-cancer pain, who may have no other effective treatment options, but the extensive efficacy evaluations could provide new insights into the long-term benefits of ER/LA opioids.

The protocol includes multiple efficacy endpoints. The range of efficacy endpoints enables the study to deliver results that thoroughly assess the long-term of an ER/LA opioid and may aid interpretation. If all of the results point in the same direction, the secondary endpoints would then tend to reinforce the primary finding; plus, if the results are positive across endpoints, they enhance interpretability. For example, the primary endpoint is the time to loss of efficacy. A secondary endpoint is pain score. Pain score may be an easier finding for clinicians to interpret than a Kaplan-Meier plot comparing time to loss of efficacy.

So if they both point in the same direction, their results are complementary and help prescribers understand the benefits of extended treatment. In contrast, discordant results across endpoints could limit interpretability. For example, the study could show that ER/LA opioids have a longer time to loss of efficacy, but that they do not have lower pain scores. It would be

difficult to interpret that result.

Another consideration is the population the trial seeks to enroll. By including participants with multiple pain conditions, the study expands the population of participants who are eligible to enroll in the study. This may help overcome enrollment challenges compared to a study evaluating participants with only one pain condition. In addition, by studying multiple pain conditions, Study 3033-11 should have enhanced generalizability. This will make the results of the study easier to interpret. On the other hand, including multiple pain conditions creates challenges, too.

For pain endpoints, there's the potential for multiple confounders that are not addressed in the randomization. For example, the inclusion of multiple chronic pain diagnoses may also introduce variability. There may be differential changes in the underlying pain condition of each participant, and those changes may not be distributed randomly and could be related to the different pain types

studied. In this way, for example, there could be differences in the underlying pain conditions that are neurogenic in nature versus those that are musculoskeletal, and these changes could vary over time differently across different pain types.

In addition, it's difficult to control for exogenous factors that may influence the experience of pain such as concurrent depression or anxiety. A standard way to control for these potential problems is to stratify participants into the two treatment groups based on the type of pain they have or the presence or absence of psychiatric comorbidities; but it's not feasible to control for every potential confounder because adding stratification variables usually requires substantial increases in sample size.

Participants will be allowed to continue their concomitant non-opioid pain medications. These include adjuvant therapies such as anticonvulsants and antidepressants, as well as over-the-counter medications such as NSAIDs. They're also permitted to continue

non-pharmacologic pain therapies such as behavioral therapy, physical therapy, electric stimulation, and yoga.

This approach has two key advantages. It should make enrollment and retention goals easier to meet, plus it better reflects real-world clinical practice in that most patients receive multimodal therapy for their pain. On the other hand, the disadvantages are that it may increase variability and efficacy outcomes. This could make it more difficult to discern an effect of the ER/LA opioid because the benefits of the additional therapies could obscure the effect of the opioid.

Study 3033-11 presents an opportunity to generate level 2 evidence of the 52-week efficacy of ER/LA opioids with a randomized, double-blind, placebo-controlled trial. The interpretation of the study results must take into consideration specific aspects related to the design, as would be true for any study design.

This protocol is a scientifically and operationally robust approach to evaluate the

persistence of efficacy during the final weeks of the year of treatment. As with any single trial, the results will need to be independently replicated. The study includes multiple assessments that will provide a thorough evaluation of the long-term efficacy of opioids. If they all align, they will enhance the robustness and interpretability of the results, but if the results are divergent, the study may become difficult to interpret.

The study allows participants to enroll with multiple different pain conditions which should enhance both recruitment and generalizability. On the other hand, variability across pain conditions or differential changes in pain over time could introduce confounding and bias toward type 2 error. Similarly, allowing patients to continue on multimodal pain therapies may enhance both recruitment and retention of participants and better reflect real-world care. A possible downside is that these background therapies could also introduce variability that could bias toward

type 2 error.

The potential impact that the trial results may have, both on clinical practice and the lives of individual patients with chronic pain, underscores the importance of designing a scientifically and operationally sound protocol. The 3033-11 protocol is the result of an extensive discussion with both FDA and external advisors. There are numerous aspects of the design that were carefully considered and have the potential to add to our understanding of long-term opioid therapy.

Dr. Argoff will now conclude the presentation.

OPC Presentation - Charles Argoff

DR. ARGOFF: FDA issued to OPC the postmarketing requirements for developing and completing multiple studies. All but one of these studies have already been completed. The final requirement has been challenging.

The first study was initiated but failed to recruit and retain a sufficient number of participants. OPC has enlisted multiple external

experts, several of whom you've heard from today, as well as their own internal clinical trial experts to create a new clinical trial to meet this requirement.

The 3033-11 protocol has a novel design intended to overcome many of the challenges of the 2065-5 protocol and address the evolving pain treatment landscape. Our hope is that this new design will yield results that add to the evidence base for individualizing care for patients with chronic pain.

The current design for Study 3033-11 reflects years of efforts by OPC, FDA, and external experts. It is the first trial of this design, and as such continues to benefit from additional perspective and insights. Every trial design represents a balance of factors to achieve a set of goals.

This is a novel approach designed to evaluate the persistence of efficacy during the final 10 weeks of 52 weeks of treatment with an ER/LA opioid. This specific duration arises from

FDA's requirement to assess efficacy and participants treated for a year or more, and the approach of having the extended 42-week open-label run-in period minimizes potential duration of exposure to placebo for this population of participants with pain severe enough to warrant ER/LA opioid therapy. The hope is that this trial will yield results that add to the evidence base regarding the use of ER/LA opioid therapy in chronic pain. As a clinician, these results have the potential to enhance my ability to individualize the care of my patients.

OPC is dedicated to collaborating with FDA to generate data that will inform the appropriate long-term use of ER/LA opioids in the interest of patients' well-being and the public health. The study before us today has been created with this in mind, and we would appreciate the insights of the committee on the proposed protocol.

In addition to the presenters you've already met, we have with us today additional external experts who are available to address your

questions. They are Dr. Jeff Gudin, who is a professor in the Department of Anesthesiology, Perioperative Medicine, and Pain Management at the University of Miami, Miller School of Medicine; Dr. Richard Rauck, who is the president of the Carolinas Pain Institute and the Center for Clinical Research, and he has treated and studied pain for over 36 years; Dr. Nathaniel Schuster, an associate professor at the Center for Pain Medicine and Department of Anesthesiology at UC San Diego Health, where he treats patients, conducts research, and educates medical students, residents, and fellows; and Ben Vaughn is the chief strategist for Biostatistics and Protocol Design at Rho, a contract research organization, and he is the statistician for the 3033-11 protocol.

Thank you so much for your attention, and we welcome your questions and discussion.

Clarifying Questions for OPC

DR. BATEMAN: Thank you.

We will now take clarifying questions for Opioid PMR Consortium. Please use the raise-hand

icon to indicate that you have a question and remember to lower your hand by clicking the raise-hand icon again after you've 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 to the next panel member.

So I'll start us off with a question, and this is directed to Dr. Katz or Dr. Comer.

I am concerned about the issue of dropout prior to randomization. If patients are doing well during the run-in period, the open-label phase, is there a concern that that they will not agree to be randomized where there's potential, and they'll be tapered to placebo? I guess I'm concerned about,

one, the implications for meeting the randomization targets, and then, two, that the people who drop out may be the ones who are actually doing best on opioids, so it may be a form of selection that biases the results or at least clouds interpretation.

I don't know if Dr. Katz or Comer can comment on that issue.

DR. ARGOFF: Thank you so much for your question, Dr. Bateman.

Dr. Katz, can you start the response, please?

DR. KATZ: Sure. Nathaniel Katz.

I'm hearing probably two pieces to your question. One is do patients drop out along the way during this open-label period, and who do you have left by the time they get to randomization? And secondly, I'm hearing you ask about whether patients who present themselves at the time of randomization, whether they might ever decline, just say, "No, I'm not going to be randomized, I'm dropping out, I'm happy on my drug," or whatever

their reason might be.

In terms of your first question, yes, people do drop out along the way in the open-label period. We know a lot about that from the EERW studies that have been done to date, although none are as long as this one. Typically, you have about 60 percent of patients left at the time of randomization, and those patients, yes, they're not the same as the ones that started. Those are the patients who tolerate the medication and who also at least appear to be benefiting from it. And that's the population that we're interested in here, so that that makes sense in terms of the question for this study, which is, among those people, is the drug really still working or not?

You rarely see a patient that says, "Gee, I'm doing so well on opioid therapy, I think I'm just going to leave the study and take my chances out in the real world." Patients are quite happy to continue to get care, and attention, and free medication and all that, in the context of the clinical trial.

So I hope that addressed the first part of your question, and in terms of the second part, you just don't see it. There have been thousands of patients randomized in these EERW studies. They know what they're signing up for when they get into it, and patients who don't think that that would be acceptable for them at the time, they don't seem to sign up. And to have a patient come for the randomization period and say, "Sorry. I changed my mind, I'm not open to be randomized," yes, you think that that could happen, but in practice, it really doesn't seem to.

DR. BATEMAN: Okay. That's helpful. And then just one other question, Dr. Katz.

I understand that the goal of the trial is to be guideline concordant. If you look at the CDC guidelines around prescribing of opioids, the recommendation is that patients be maximized on non-pharmacologic or non-opioid pharmacologic agents before chronic opioid therapy is considered. So was there thought given to whether that should be an inclusion criteria, and if not, is there

concern around the ethics of enrolling a patient into a trial of chronic opioid therapy who hasn't been maximized on non-opioid alternatives?

DR. KATZ: Back to you, Dr. Argoff, for this one.

DR. ARGOFF: Thank you so much, Dr. Katz.

I think what's really super important -- thank you so much for the question, Dr. Bateman -- is, in fact, we are consistent with the CDC guideline in the inclusion criteria, and it's the reason why we developed the PTRQ, which is a questionnaire that focuses on establishing, to the fullest extent possible -- you can put up slide 2, please -- which focuses on looking at what alternative treatments have been offered to a patient, to a potential participant.

This is being done before screening so that we can be in sync with the point you just made about there having been established multiple attempts across multiple treatment domains, both pharmacologic and non-pharmacologic, in addition to trying to obtain medical records, looking at

prescription monitoring program details as well, and other data, to assure that we are looking at a population of individuals who not only have had a trial of IR opioids and still have severe pain, based upon the study protocol inclusion criteria, but also would otherwise be considered ready for a trial of an ER/LA opioid.

If you could bring up slide 2 again. This is just another schematic to really emphasize how seriously we take this in trying to find the most appropriate population to fulfill this PMR.

DR. BATEMAN: Just to make sure I understand this, is that a requirement for enrollment, that they've tried other therapies and found those to be ineffective or --

DR. ARGOFF: Yes. Yes.

DR. BATEMAN: -- it's just collecting --

(Crosstalk.)

DR. ARGOFF: Yes.

DR. BATEMAN: Okay. It's a requirement.

DR. ARGOFF: Oh, no. It's absolutely a requirement, yes.

DR. BATEMAN: Okay. Thanks.

DR. ARGOFF: That's part of our strategy in defining who would be considered an appropriate candidate. Absolutely.

DR. BATEMAN: Okay. Thank you.

The first question, Dr. Ness.

DR. NESS: Hi. Thank you. I'm Tim Ness from University of Alabama at Birmingham. I actually have two questions. The first one is for, actually, Dr. Katz or Argoff, and it was related to the blinded taper, component of it.

Was there any consideration given to trying to control for expectations related to the taper? Because this tends to be a very hypervigilant population. You're starting to ask them to do all these daily sorts of pain measures, and I can tell you from personal experience with withdrawal trials, almost a hundred percent of them are sure they're being tapered off of the medicines.

My question would be, then, did you think about putting like a 2-week period, where they're actually not tapered off of the medicines to begin

with, which would mean that it's not changing the taper of medicines but it would be assessing for what the expectations of the patient were related to that taper? That's my first question.

DR. ARGOFF: That's a very interesting question, and I believe Dr. Katz has actually done a lot of work in this area, so I will ask him to respond.

DR. KATZ: Yes. Thanks. Nathaniel Katz. Yes, it's a wonderful question. The short answer is no. There's nothing in this protocol right now about evaluating expectation, but I understand what you're asking about and why, and I think it would be interesting, personally, to add a measure of expectation, for example. In fact, I was just an author on a paper that very recently came out about this. Yes, a lot of us are very interested in the role of expectation here.

As an indirect response to your question, we are proposing including a blinding questionnaire at the very end to ask patients which group they thought that they were in to address the potential

concerns about functional unblinding, and it's not indirectly related to expectation, but direct assessment of expectation I think would be interesting.

DR. NESS: Yes. I guess my concern is, if your primary endpoint is they're going to withdraw from the study, and their expectation is they're being tapered, and so they would withdraw, I would want to control for that before the actual taper happened in those sorts of things.

I did have a quick second other question, and this one was actually to Dr. Angst. It was just related to the quantitative sensory testing. Your reviews and everything else show that there is a very significant modality-specific type of thing for what type of pain was being tested and how hypersensitive people become.

Was consideration given also to doing things like the cold pressor test? It actually has pretty good literature related to opioid-induced hyperalgesia. It's quick. It wouldn't add a lot to your protocol. I mean, the thermal makes a lot

of sense, but were there any other modalities you considered?

DR. ANGST: Thank you for that question. This is Martin Angst. Yes, we did consider other modalities, and specifically modalities -- you just mentioned the cold pressor test that has been used in cross-sectional studies, mainly in the abuse and addict population.

There is one prospective trial that randomized patients with chronic back pain to opioid treatment or placebo. That particular trial actually used the cold pressor test. While the trial was able to demonstrate the development of tolerance, the cold pressor test was not sensitive to capture signs of opioid-induced hyperalgesia.

Could we bring up slide 297?

The rationale for proposing, as you pointed out, probably is more complicated. A QST algorithm using some special equipment is really accurate in studies that have been done in patients, chronic pain patients, who are on opioids or not on opioids, and one of these studies is summarized on

that slide. What the study demonstrated was that chronic pain patients on opioids have an increased sensitivity to heat pain compared to the chronic pain patients not on opioids, and interestingly, this was dose dependent. So that's the major rationale why we eventually decided to use thermal pane.

DR. NESS: Thank you very much.

DR. BATEMAN: Dr. Brittain?

DR. BRITTAIN: Hi. I'm Erica Brittain. This was an excellent presentation. Thank you for that. My question is for Dr. Katz as well, and it's kind of related to the first question.

Again, I do think this is a really interesting design, but I am worried about the potential for unblinding during the randomized phase, partly because of side effects, and I didn't hear a lot of concern about that in the presentation.

Are you not concerned that people will know in the placebo group that things are changing, and thus, they're in the placebo group?

DR. KATZ: Yes. That is an issue that comes up a lot when people are evaluating these sorts of designs, and we do think about that. I think what I would say is that, yes, it's an issue; we have to think about that. Of course, it's also an issue in any other kind of design. If you take patients who have had experience with opioids and you prospectively randomize them to an opioid or placebo, it's not that those alternative designs are free of such concern.

I will say that the issue of whether functional unblinding occurs in pain studies and whether it matters in terms of the outcome has been looked at a couple of times, three that I can think of. There were a series of papers that came out in the early 2000's, mostly from Mitchell Max's group at NIH. I don't know if you knew him.

He looked at two different crossover studies, looking at things like lorazepam, and opioids, and antidepressants, things that actually have a lot of side effects, and they looked at, number one, whether their patients could guess what

they were on; number two, whether healthcare providers could guess what they were on; and number three, whether any of it mattered for the between-group difference that was observed in the clinical trial.

The answer, at least from those two explorations, was that it really didn't seem to matter. Despite the fact that you'd think that patients would know what they were on, most patients, their guesses were no better than chance, and it didn't end up mattering for the results of the trial. That doesn't mean that it can't be relevant here. It could be, and that's why we've decided to put in this unblinding questionnaire at the end, just to do forensics afterwards and see if it ended up mattering, but so far, to date, when it's been looked at, perhaps surprisingly, it doesn't seem to make much of a difference.

DR. BRITTAIN: Yes. Again --

DR. ARGOFF: Dr. Brittain, may I add to that response just for a sec? Would you mind?

DR. BRITTAIN: Pardon me?

DR. ARGOFF: May I add to that response? This is Dr. Argoff. I'm sorry.

DR. BRITTAIN: Sure.

DR. ARGOFF: You made another point, which I wanted to add to the response, is that during the withdrawal phase, individuals will have access to rescue medication, including acetaminophen and immediate-release morphine, up to 30 milligrams per day of the immediate-release morphine. And also, the manner in which we're tapering individuals is over a longer taper than is typically done in a placebo-controlled trial for FDA registration purposes. So we're trying to take those concerns into account.

DR. BRITTAIN: Okay. Thank you.

DR. BATEMAN: Dr. Bicket?

DR. BICKET: Thank you. I'm Mark Bicket at the University of Michigan. My first question related towards Dr. Argoff or Dr. Katz about the protocol development, and just following up on Dr. Bateman's earlier question about some of the concerns about patients not wanting to taper off

their opioids once they're on a stable dose.

I just wondered, with this current change with the protocol, if there was an opportunity to engage with persons who have chronic pain, whether they were on opioids or not, and if they had commented on the protocol, whether it was through focus groups or other things, and how that feedback was incorporated, if it was there.

DR. ARGOFF: This is Dr. Argoff. When we have developed this protocol, we have not reached out to focus groups with chronic pain patients. I think that it is an excellent suggestion, and upon the input of this committee and further discussion with our colleagues at OPC and FDA, as we go forward, we do plan to have focus groups of various types to assess the feasibility of the protocol once finalized.

DR. KATZ: If I may, Dr. Argoff, I do want to add that for the original 2065-5 study, at FDA's suggestion at a public meeting on that design, that I think was in 2014, we did do a qualitative study of patients with chronic pain with and without

opioids, to ask them what they thought about the last EERW study. And we did learn quite a bit from that experience, and that did result in some modifications to that protocol, basically, to encourage recruitment and retention; although, as you've heard, the complexities and burden of the protocol still overcame whatever changes that we made. But we have done that and certainly could benefit from doing that again.

DR. BICKET: I appreciate those responses. My follow-up question is on a different topic about the tapering methods. This was mentioned in the protocol documents. I think it was section 5.2, or I think, Dr. Katz, you've mentioned this on slide 41.

I wondered if you would be able to comment on the prior studies that informed the tapering approach as it related to the duration of the opioid exposure for those studies, and if those were similar to those in this study, and if you saw that length of the opioid exposure being relevant to the length of the tapering period here, with

full transparency, seeing 3033-11 being much longer in duration than perhaps some of those prior studies. But I just wanted to check to see if that was the case and if that was a concern. Thank you.

DR. ARGOFF: Dr. Katz, can you answer that, please?

DR. KATZ: Nathaniel Katz. I can take a crack at that. What I can tell you is that in the prior enriched enrollment randomized withdrawal studies that have been done -- and there are about 2 dozen of them -- those studies have involved both opioid-naïve patients that come in either on nothing or on just a smattering of IR opioids, and they've put an extended release, or opioid-tolerant patients who come in already on substantial doses of an ER/LA opioid, for example, and then are stabilized and randomized. Sometimes they're studied separately and sometimes they're mixed together in the same study, and people have come in on quite high doses in some of those past studies.

Then in terms of the tapering periods, usually in past studies, I have to tell you that

they've been very rapid, a few days, a week, 2 weeks, something like that. Patients have been brought down, sometimes from very high doses, to placebo in relatively short periods of time, and usually with access to rescue medication just for a short period of time, a week or two. And despite that, even in the studies on opioid-tolerant patients, the incidence of patients having a discernible withdrawal syndrome, it's always been very low. I think the highest was 6.9 percent, as I recall, but generally it's like in the 1-2 percent range.

I don't think that anybody has looked specifically at the heart of your question, which is, do you look at people based on their duration of pre-study opioid exposure to see whether they once were more likely to go into withdrawal? I don't think anybody's actually done that, but the general experience is as I've described, and hopefully that's helpful to you.

DR. BICKET: Thank you.

DR. BATEMAN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: HI. Thank you. Elizabeth Joniak-Grant. I have a few questions that I wanted to ask. The first one is -- and this might be best for Dr. Katz -- how are you accounting for the phenomenon with chronic pain patients of good weeks and bad weeks, good months and bad months? Using this worst pain intensity score, it seems like it's just, if I'm understanding correctly, the previous 7 days. So how are you managing the fact that pain often has variability?

Also, for example, worst pain intensity might be stable, but the individual may be doing more because they're feeling better. So how did that factor into the structure of the study?

DR. KATZ: Dr. Argoff, may I?

DR. ARGOFF: Yes. Please go ahead. It was directed towards you; of course.

DR. KATZ: Sure. Nathaniel Katz again.

You're right; patients with chronic pain, their clinical course is typically one of waxing and waning. They'll have good months and bad

months, and good weeks and bad weeks, and good days and bad days. That is all true. We used to do pain studies by just capturing their pain intensity literally on the last day of the study, and that led to questions about, "Well, how many days do you need in order to characterize somebody's stable chronic pain state?"

There were a number of papers that came out examining that issue in the early and mid-1990s, one from actually my group at the Brigham and another one from Mark Jensen at the University of Washington in Seattle, and both papers found that if you have poor scores in the course of a week, then the conclusion was that that's generally representative of the patient's chronic pain state around that time.

Now of course, the patient could have had a bad month before -- well, I guess I should say, for that reason, generally speaking, these days in chronic pain studies, the best practice is looking at daily electronic time-stamped diaries and averaging the scores over the course of the final

week of the study, and then looking at the change from baseline. However, to your point, we also will have the ability to look at the patient's daily scores throughout the course of the entire clinical trials, and particularly during all 10 weeks of that 10-week post-randomization period, and if there were any fluctuations or important time trends over that period of time, we'd be able to discern that as well.

Did that hit all the aspects to your question?

DR. JONIAK-GRANT: Yes, it does. Thank you. I'm understanding that there would be daily scores, and that you could kind of track trends was helpful.

My other question is, was it ever considered to not taper the participants who are stabilized and receiving ER/Las and are assigned to the ER/LA arm of the study to get them in so they wouldn't have to taper off, and then find another healthcare provider and try and perhaps get back on; and why or why not?

DR. ARGOFF: Dr. Katz, can you please take that one, too? Just in a brief response -- this is Charles Argoff again -- as a prelude to Dr. Katz's response, we gave a lot of thought to that question, so thank you for that question.

DR. KATZ: Yes. We debated about that as well, and in fact, to be honest with you, are still debating about that. You're right, in the sense that from the patient's perspective, if the patient is stabilized on a substantial dose of the ER/LA opioid, they may not want to come off, and it might be in their interest to just transfer to their primary care doctor's hands and have that continued.

On the other hand, we also spent a lot of time thinking about how to ensure that the patient would in fact have a doctor to transition to at the end of the study, who could take over, and they just wouldn't be left hanging at the end of this one-year clinical trial.

The problem is that we have limited control over the real world, and there's a lot of churn in

this space. In fact, no matter how hard we try, we can't guarantee 100 percent -- and the patients will be informed about this -- that their doctors are going to be waiting for them with open arms a year later. And for that reason, the taper was put in for all patients as a safety measure, basically, to ensure that patients would be safe and not be left hanging on a high dose of opioids without anyone to prescribe for them. But if there's a better way of doing it, today's the day where we'd love to hear feedback on that, but that's the rationale.

DR. JONIAK-GRANT: Okay.

Then my third question is for Dr. Angst. How do you distinguish opioid-induced hyperalgesia from the development of fibromyalgia? Because all the criteria sound very similar.

DR. ARGOFF: Dr. Angst, can you please take that question?

DR. ANGST: Yes, I'm happy to take that question, and thank you for the question. I think you you do address an important confounder. Now,

fibromyalgia patients, I think fibromyalgia -- I want to refer back to Dr. Argoff regarding inclusion criteria to the study -- are not included in the current study population.

DR. ARGOFF: And that is a primary diagnosis.

DR. ANGST: So it would be sort of a new onset of it, but as a confounder, that limits the confounding influence.

But I would also say, regarding your question, obviously some of the clinical endpoints used, like widespread pain, you're right; that's not necessarily specific to OIH. That could be a flare. There are other reasons that could explain that. That's why I do think the inclusion of QST will allow us to make some distinction. But the development of hyperalgesia, particularly in the context of fibromyalgia, I would agree that could be a potential confounder if this patient population is included.

DR. JONIAK-GRANT: Okay. Thank you for that

Then my final question is, in looking

through the materials, it's kind of lacking details on the patient experience in the study. I was wondering if someone could speak to, a little bit, about what these assessments would look like in terms of time commitments and how frequently in person. There's a lot of mention of remote contact. How frequent is that and what does that involve? There's mention of diary entries. Hw are those done?

Then also, managing investigator bias, there was a lot of talk about if a urine drug test papers came back with a potential issue, they should respond non-judgmentally, but then when you look at the charts for here's all the possible explanations, they were all very leaning towards the patient was up to something problematic.

So if you could speak a little bit more to -- because in understanding feasibility, what are these patients actually asked to do beyond taking this medication and then perhaps not taking it? Thank you.

DR. ARGOFF: Sure. Thank you for that

excellent question. This is Charles Argoff. If you could bring up study 1. Thank you.

To your point, there are multiple assessments at multiple times, so I'd like to not only discuss them verbally but also show some assessments through the slides so you'll get a sense. The short answer to your question is that this is a commitment of both the patient as well as the investigator to accomplish this trial. There is quite a bit of involvement and assessment, and this is really designed, of course, to meet the goal of the study.

So a list of study assessments are seen on the slide that I've asked to come up. These are only a partial list. If you can bring up slide 1, this gives you an idea of the different phases of the study beyond the screening and some of the assessments and scheduled assessments, ranging from remote contact to in-person contact, obtaining demographics and medical history.

If we could see slide 1 again, please, this is a second of four slides regarding the

assessments, and it certainly is in the protocol to be looked at as well, but this gives you an idea of the assessments.

If it we could see slide 2, please; slide 2 up. This is the third of four sides regarding this and at different stages. It's so hard to go through each one. I can if you'd like.

Slide 3, please. So to your point, there will be times when a person is being contacted daily, and weekly visits, and during the randomization phase, there are every 2-week visits with remote contact in between. But the goal, of course, is to achieve the goals of the study, and we have included these time points, and checkpoints, and assessment strategies to enhance our ability to arrive at an answer to what the question's being asked.

So I hope that answered your question, not completely, but to give you an idea of the flavor.

DR. JONIAK-GRANT: Yes. I think one comment with that is it'd be really important to be mindful of when in the appointment the QST testing, if

that's done, is done; because all I can think of as a chronic pain patient is how many hours would an individual be sitting there, and how much worse would their pain get while they're sitting there doing all these assessments.

DR. ARGOFF: That's a great great question.

Dr. Angst, I wonder if you can comment about how you have helped us to develop that part of the protocol.

DR. ANGST: Yes. It's an excellent question. Patient burden is a really important consideration in the study design. We try to limit the sessions of QST to basically six occasions. And with respect to the length, we design the protocol that we think can be accomplished in about 40 minutes. Part of the initial phase of the study will actually be a feasibility study. We will address exactly that question, how long does it really take to do these tests in these pain patients? There is operation in the current QST protocol to abbreviation the protocol should that be necessary. The goal would be to limit the QST

session to a maximum of 40-45 minutes.

DR. JONIAK-GRANT: Thank you.

DR. KATZ: Dr. Argoff, can I add a comment?

DR. ARGOFF: I just wanted to add one comment before you add your comment, Dr. Katz, and that is, in response to the last question, OIH is being assessed through QST as a substudy in 200 patients of this population at select sites, just to emphasize that point.

Yes, Dr. Katz?

DR. KATZ: I was actually going to say the same thing. I'd just remind everyone that only a subset of sites and a subset of patients will participate in the OIH piece. I also wanted to mention that the urine drug testing occurs three times. It sounds like you were asking about that. There are three of those during the course of the clinical trial, and that's also balanced between testing more in order to monitor patients' safety with respect to drug, but testing less because it's burdensome, and happy to receive feedback about that today as well.

Finally, the more people you involve in the design of a protocol, the more assessments you end up with. That's just how it works. And yet, at the same time, we know that protocol complexity is a problem, and the more endpoints you have, the less likely you are to achieve the important one. So if the committee today has any recommendations about protocol simplification, we'd be delighted to hear those as well.

DR. ARGOFF: And one other additional point just for reference, pages 62 to 66 of the FDA briefing document has all the assessments. Since there are many, you might be able to look at them in more detail.

DR. BATEMAN: Thank you.

We're about 10 minutes before the break, so I'd ask the the advisors that have questions to please just limit to single questions, and we'll try to get through as many as we can before the break.

DR. SPRINTZ: Hi. This is Michael Sprintz. Actually, I do have two important ones, the first

one being the question, one, that it was a great presentation, and I think the way that you're designing this study is the best that you can given the situation, but one of the questions that I had was these are patients who are unsuccessful in any other therapy.

So we've got patients who've already failed everything else or not doing great on everything else. I know that you're doing the POMAQ, but you mentioned that you're getting the histories from the patients and everything seems self-reported. What are you going to do about assessing the history? I know, Dr. Argoff, you mentioned the PDMP, but what about non-controlled substances?

These are the patients that I'm concerned, ultimately long-term, especially during the taper, that they're going to end up using something in order to tolerate the taper, and that's a big concern of mine, and that relates to the drug testing part as well. So my one question was how you're planning on confirming that? And I do have a suggestion for the drug testing.

DR. ARGOFF: Well, I greatly appreciate this very, very important question, and if I could ask you what your suggestion is because we've considered -- from a practical point of view, you've brought up a very important point we don't know what people are doing if we don't know what people are doing, and they may be doing things we don't know that they're doing.

DR. SPRINTZ: Yes.

DR. BATEMAN: So let's stick to clarifying questions for now, and later we'll have an opportunity to --

DR. SPRINTZ: Okay. So my clarifying question was, in terms of assessing objective assessments for the patient's previous use of medications, or current use of medications, or other uses, you mentioned the PDMP, but how are you managing other medications, or how are you confirming those things?

DR. ARGOFF: Sure. Within the written protocol, under that section, we do -- so I'm going to read from it so that it's clear. So I am

reading from it, just to be clear, what's in the protocol?

"The PTRQ will be reviewed by the investigator in conjunction with other external documentation such as medical records, monitoring data, or claims data as available to confirm that patients are appropriate candidates for ER/LA opioid therapy. Investigator completed forms associated with the PTRQ will provide investigators with guidance on definitions of prior treatment failures for each indication."

So it's not perfect, as you have pointed out, and we are trying our best to capture that information with the knowledge that in any setting, clinical trial, or patient care, it's not possible to get all information at all times.

DR. SPRINTZ: I gotcha.

Okay. And then, Dr. Katz --

DR. BATEMAN: Dr. Sprintz, we'll circle back to you if we have time. I want to move on to some of the other panelists.

Dr. Horrow, please.

DR. HORROW: Jay Horrow, industry representative. I have a clarifying question about the primary endpoint.

Dr. Bateman asked about dropouts that occur prior to randomization. I'm asking about dropouts that occurred during the randomized trial phase. One of the components of the primary endpoint, which constitutes failure, is study withdrawal. There are competing risks to study withdrawal such as not-opioid-related deaths, development of cancer, heart disease, MI, stroke, PCI, et cetera, that can occur over the course of 10 weeks and would lead to a patient withdrawing. I expect among the 400-plus patients, there will be a number of cases.

The draft protocol is scant on information relating to the policy on handling these intercurrent events. They appear to constitute non-informative censoring, and my question is, are they considered when they censor as treatment failure or are they censored as non-failure?

DR. ARGOFF: Thank you very much for this

question. I'd like to ask Ben Vaughn, our study statistician, to take the first chance at answering this question.

MR. VAUGHN: Sure. I'm Ben Vaughn. I have been compensated for my time. I have no financial interest in the sponsor companies or the outcome of the meeting.

Currently, we are treating those as non-informative censoring. We do acknowledge that they are informative about how the patient is doing; however, they may not be informative about the efficacy of the drug. So our current handling of those will be that they are censored at the point that they drop out from the study or we don't have further information on them for the components of the primary efficacy endpoint.

DR. HORROW: Excellent.

MR. VAUGHN: We do look forward to your input on that.

DR. HORROW: Excellent. Thank you. That's the end of my question.

DR. BATEMAN: Thank you.

Dr. McAuliffe?

DR. McAULIFFE: Maura McAuliffe, East Carolina University. My question is about the rescue opioids, and either Dr. Comer or Dr. Argoff probably could answer this for me.

Are you requiring the patients who use rescue opioids to document in any way any change in pain intensity when they are using the rescue opioids? And my question is, that may have an effect, especially during the randomized withdrawal, in the placebo group. So are you looking at that in any way during the trial, and then into the placebo aspect? Thank you.

DR. ARGOFF: So if I could clarify your clarifying question, are you asking when they take the rescue medication, are we asking them to document what their pain and [indiscernible] level is before and after?

DR. McAULIFFE: Yes, so that you can get some sense of is it waxing and waning, or is it breakthrough, and how would that carry through.

DR. ARGOFF: Or a flare or something like

that. So the short answer to your question is, yes, we are.

DR. McAULIFFE: Thank you.

DR. BATEMAN: Thank you.

Dr. Jowza?

DR. JOWZA: Hi. Thank you. Maryam Jowza from University of North Carolina in Chapel Hill. I have a question about the inclusion criteria for the study, if there is consideration for including patients who previously may have been on chronic opioid therapy and have seized treatment for years, or perhaps have been on it for a prior condition, and now to be included in the study; would those folks be allowed in?

DR. ARGOFF: Are you asking if a person who had been previously -- thank you for question. I just want to clarify that you're asking if someone had been, say, five years ago on a treatment with opioid therapy, and otherwise met current inclusion criteria and did not have any exclusion criteria for being part of the study; have we included as an exclusion criteria as treatment with opioids in

their remote past?

DR. JOWZA: Correct.

DR. ARGOFF: Okay. The answer is no, we have not excluded those --

DR. JOWZA: Okay. Thank you.

DR. ARGOFF: But the bottom line always, as is common with -- well, it's subject to the investigator looking at the totality of that situation, but we have not specifically excluded those people.

DR. KATZ: May I add a comment to that, Dr. Argoff?

DR. ARGOFF: Yes, of course, Dr. Katz.

DR. KATZ: Just to be crystal clear, inclusion criteria, and number 4 in the protocol, is that the patient has to have been on daily, short-acting opioid therapy for at least three consecutive months in the past 6 months, with an inadequate analgesic response. So if they were on short-acting opioid therapy for 3 months 2 years ago, that would not be adequate to get them included. It would not exclude them as long as

they did meet the criterion of also having been on opioids for 3 months in the past 6 months.

So if folks on the committee have advice or feelings about that, then that would be good to discuss, as well.

DR. BATEMAN: Thank you.

We're right on time, so we'll now take a quick 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 will resume at 11:30 Eastern Time.

(Whereupon, at 11:20 a.m., a recess was taken, and meeting resumed at 11:30 a.m.)

DR. BATEMAN: Okay. We'll now proceed with the speaker presentation from Dr. John Farrar.

Speaker Presentation - John Farrar

DR. FARRAR: Good morning. This is Dr. John Farrar. I'm a professor of neurology and epidemiology at the University of Pennsylvania, and I'm here today to talk to you about enriched enrollment randomized withdrawal trials, designs

for studies in chronic pain. But I'd like to start by declaring that the opinions expressed in this presentation are mine, and not those of the University of Pennsylvania or the FDA.

The topics for this presentation will be the concepts underlying EERW studies, including advantages and disadvantages, and potential uses, and issues to consider, including internal validity, external validity, or generalizability, and the importance of inclusion and exclusion criteria.

In defining the purpose of any clinical trial, we need to consider why we do such trials, which is to answer a specific question. The selection of the design must focus on the question to be answered, including the population, exposure, and outcome. No single study will answer all questions, and every study has advantages and disadvantages with underlying assumptions that must be understood to properly interpret the results. EERW studies are no different.

In this diagram of some standard approaches

to clinical trials, we can consider the parallel clinical trial in which the enrollment of patients are limited to exclude patients with significant psychosocial or medical illness that might put them at risk or participation in the trial, and in the case of opioid trials, excluding patients with opioid-use disorder.

Once enrolled, the population is randomized into two groups, one of which is treated with the new therapy and the second of which is randomized to the comparison group, very often a placebo group. These are followed over time, and differences are noted between the groups.

Crossover designs are a similar design with an initial randomization, followed by a period of withdrawal of therapy, and then a cross over to the opposite group or another observational period. One of the problems with this study is the potential for carryover effects such that if there are any long-term effects of the therapy, this design is not appropriate; however, when it is appropriate, the within-person comparison is a very

efficient way of conducting clinical trials.

An enriched enrollment randomized withdrawal trial -- slightly different -- in the screening period, the inclusion and exclusion criteria are identical to those of other clinical trial designs, but those patients enrolled go through a titration period often preceded by withdrawal from their previous medication and the achievement of response in patients that are able to tolerate the drug.

Patients that do not respond to therapy or who have side effects that result in their dropping out are not included in the continued randomization period. Patients who have responded are randomized to either continue on the active therapy or to be titrated down and off the therapy of interest into a placebo group. The expectation is that patients titrated to the active group will maintain a response, whereas those titrated off the drug will lose their response over time, providing a difference between the groups that is the result and provides us with the results of the clinical trial.

Here's an example of a buprenorphine study where the screening period was 2 weeks, followed by analgesic taper of 4 weeks, and then a titration on to an effective dose of 8 weeks. For those patients who achieve an effective dose without significant side effects, they move to the randomization phase, where they are randomized to either remain on the buprenorphine or to be transitioned to placebo, and the differences in the response between the two groups is ultimately the outcome of the study.

Before considering more details about study design, it's worth thinking about the effect size comparison of randomized trials for pain. In this study by Roger Chou and authors, they found that parallel trials conducted since 2007 had a mean difference between treatment and placebo group of minus 0.66. Interestingly, trials before 2007 reported larger differences in the order of minus 1.12. The reason for these differences over time is unclear, although there are a number of suggestions that increase in the placebo rate may

be a part of the difference.

Crossover trials over the same periods have larger differences in general with a value of minus 1.19, and EERW studies, almost all of which have been conducted since 2007, had larger differences as well, at a level of 0.81. In considering EERW studies, it's important to think about the design issues that go into all RCTs since there are a number of similarities.

All clinical trials, as we've said, are designed to answer a specific question. Parallel randomized trials are intended to remove most of the baseline bias in confounding, resulting in equal groups to allow the differentiation between the effects of treatment and placebo to be found. The population homogeneity may limit broader generalizability, depending on how homogeneous the population is that's selected.

Crossover trials have the same homogeneity issue, but are highly affected and efficient in their analysis because the participants serve as their own controls. However, as we stated before,

there are potentially issues of carryover and time effects such that it's best used for medications that have relatively short effects in time.

Potential problems with all randomized trials is that it's not ethical to randomize patients to many exposures. The population selection and choice of phenotypes can be difficult to identify, and then dependent on how restricted it is, the recruitment may be problematic. There's also evidence that patients are less willing to enroll in clinical trials if there's a placebo-controlled group.

Randomization, which is the key feature of all randomized trials, needs to be preserved and best done by a centralized office to preserve blinding. Dropouts and missing data are always issues, and as we've talked about, generalizability can be an issue. For pain studies, the need to account for rescue is another issue to consider.

Clearly, in randomized trials, blinding is a key issue, and careful blinding of the control group, especially a placebo-controlled group, is

intended to limit the participants' expectation of effect, and it's more effective if participants and study staff are unaware of the the groupings and are unaware of the timing of the potential placebo exposure. Unblinding from side effects is also a potential issue that must be considered.

Blinding is not always possible as in surgical trials, and it's important to realize that the randomization remains, in fact, a good control of bias and confounding, but what is being studied and what's being compared instead of the treatment to placebo is the treatment with the knowledge of the treatment to the untreated group with the knowledge of the untreated status. It's a valid comparison but has issues related to how its applicable to clinical practice.

In thinking about enriched enrollment design studies, we need to understand what it means to have enrichment. It can be looked at in a number of ways, starting with clinical care. Differential diagnosis in clinical care is the process to select patients based on history, exam, and laboratories,

which enrich the likelihood of finding the etiology of the disease causing the signs and symptoms. Even then, treatment of patients often involve some degree of trial and error, carefully following the patient's response.

For example, in hypertension, there are a number of drugs that might be used, and patients are started on an initial therapy and followed for response and side effects. Based on the response and the side effects, they may well be transitioned to a second drug or a third drug since not all drugs work in all patients. Trial and error is a common approach to the treatment of pain because of our difficulty in understanding the underlying mechanisms for many pain syndromes.

In terms of study populations, every prospective study uses an enriched population. For example, the study of angina therapy will enroll only patients with pain related to heart function and not all chest pain patients. Studies of antibiotics for upper respiratory infections will consider the fact that viral etiology is the most

likely cause, and that enrolling patients on antibiotics is only really applicable if symptomatic therapy doesn't work.

The homogeneity of the population improves the likelihood of finding an effect because of this reduction of variability, but it reduces the generalizability. EERW studies enrich the population by identifying increased likelihood of the ability to respond to the study drug, providing a better way of understanding whether patients with response to that drug ultimately incur benefit from that treatment.

Why do we need enriched enrollment studies? Our current ability to identify specific pain etiologies is limited. For example, in chronic low back pain, the etiology may stem from nerve, bone, muscle, or connective tissue. Muscle spasms may often be the predominant pain that comes about as a result of these stimuli, and when we go to treat the patient, it's unclear whether we are going to be targeting any of these specific underlying pathophysiologies.

In addition, factors that facilitate nociceptive input in transmission to the brain or the perception of that input can vary significantly. Thus, any clinical trial of chronic low back pain involves a heterogeneous group of patients and the identification of a drug that may be effective in one specific underlying etiology may be difficult.

EERW studies have the benefit of identifying a population with a phenotype with at least the potential to respond to the treatment if a true treatment effect exists. So let's consider some design issues in EERW studies. Like parallel studies, EERW studies have many of the same problems but also have some advantages, which include potentially less issues with recruitment since we treat all of the subjects with drug; the population selection is specified for patients with phenotypes that increase the likelihood of responding to the study drug; and titration period leads to less missing data after randomization. Generalizability remains an issue, but it is less

of a problem if the selection of the population is consistent with usual clinical practice, but there may be some potential issues during the drug taper to placebo after randomization.

The run-in period helps to prevent study dropouts after randomization and are consistent with clinical practice. They exclude participants likely to be unable to tolerate the treatment, which is similar to what happens when we treated patients with drugs. If they develop side effects, we stop the drug and switch to another product. It also handles the high variability that can occur in participants' response to treatment by titrating to an effective dose, similar to what we do in titration in clinical practice. The run-in period is also important as it tests the participants' willingness to complete the study procedures and reducing dropouts.

Generalizability is an issue, but similar issues occur in standard parallel studies if population to be selected is going to be homogeneous. It may be less of a practical issue

if the selection criteria for the study population is consistent with usual clinical practice, and one could argue that the exclusion of patients with significant psychological or medical risk factors without opioid-use disorder is an appropriate exclusion of patients.

The titration to an effective dose with tolerable side effects also mimics clinical practice, as I've said. The possible carryover effect is a similar effect to the crossover studies, making the design better for short-acting drugs, as is true for many of the analgesics.

EERW study designs have a potential problem with the withdrawal symptoms that can occur during the drug tapered to placebo. There are some things that we can do about this, and the first is that a blinded withdrawal is less problematic than open withdrawal because the patient is unaware of the process of the withdrawal. Randomizing the time of the start of the taper can help to reduce the expectation of the transition effects, and allowing reasonable use of rescue throughout the study is

clearly an advantage.

Extending the observation period on the stable dose after titration to allow for patients to experience natural variation in pain and the use of rescue can help mitigate the events that occur during the active transition to placebo as well, and randomizing the timing of the transition over a few weeks will help the patients not know when they're being transitioned.

It's also important to carefully blind patients and study personnel to avoid any issues with expectation of effect. It's important to measure withdrawal symptoms -- COWS and SOWS -- for opioids throughout the trial to understand any potential unblinding.

Careful collection of specific reasons for any dropouts will help to explain the results and understand whether they have been adequately obtained, and we should consider offering to patients who want to drop out of the potential to return to the previous active medication dose they were on prior to dropping out as a way of keeping

them in the study and understanding better how they respond.

Potential uses for the study design, the EERW studies are randomized assessments of the continued benefit of a drug over time in a population of patients who have demonstrated an initial response. It has the potential to be used for multiple assessments over time, if appropriate, by returning patients to study drug between assessments. An advantage of this is that although patients will know that they will be randomized to placebo at some point, they also know that they will return to the study drug following the placebo period, which encourages them to stay in the study.

Potential issues are that the primary outcome of such multiple episodes would need to be a pain level and the patient's report of a loss of efficacy, either a PGIC or a related measure; and if there are only a small number of dropouts from the study, then it becomes a true crossover design with increased power. If there are dropouts, then each randomization maintains its internal validity

because it is a reasonable study of those patients remaining in the study.

In conclusion, EERW studies are a valid and well-documented design for assessing continued efficacy in patients demonstrating drug benefit without serious side effects and is similar to how we treat patients in clinical practice. EERW studies answer the question of whether there is a group of patients in a population who respond to drug therapy and lose the effect when it's withdrawn.

EERW studies do not inform us about the results of the exposure of a larger, less well selected population, but the screening process for admission to the titration period is identical to that used in other RCT designs, and the titration period provides data about the success and rates of side effects in the population enrolled and exposed to the drug, and as such, the EERW study design is useful in the proper setting.

With that, I'll stop and see if there are any questions. Thank you.

Clarifying Questions for Dr. Farrar

DR. BATEMAN: Thank you.

We will now take clarifying questions for Dr. Farrar.

Dr. Bicket?

DR. BICKET: Good morning. This is Mark Bicket at the University of Michigan. Thank you for your presentation, Dr. Farrar. I have two questions for you. The first one related toward your presentation. I think it was back on slide 19. You had mentioned about removing individuals who were unable to tolerate treatment.

I wondered if you would be able to comment on the loss of individuals at that time point. Are we trading off selecting a very homogeneous population for losing some information about risks or adverse events, or reasons that people may not continue on in the open-label phase; and what your thoughts are if there are ways to account for that as they do relate to the study design that we're looking at for Study 3033-11?

DR. FARRAR: I agree with your point that

there is a loss of information in patients who don't tolerate the treatment, but that is information that is known from the titration period. It is probably not ethical to include them in the long-term study.

The real issue, I think, is what's the question you're trying to answer, and as I said, the EERW studies are really focused on looking at patients who tolerate drug and asking the question of whether or not, as a population, they gain some benefit from that. It is not a question about what happens if you give the drug to a much larger population. That's a completely different study design. It can be done, but it really is not the one that's being addressed here.

DR. BICKET: Thank you.

My follow-up question is related to slide 24. In reading about the enrolled enrichment randomized withdrawal designs, I have not necessarily come across this idea that with a small number of dropouts, this study becomes more like a crossover design. I apologize. I know you are

quite astute in terms of the clinical trial design, and understanding this, would you mind unpacking that? I just didn't quite understand how the enrolled enrichment randomized withdrawal then turns into the crossover or the analogy that you were making there. Thank you.

DR. FARRAR: Yes, and I present this -- I'm vacillated about whether to go this far with the study design. The point about the EERW study is that it is targeting any population of patients on a drug and, in fact, you could take patients in a clinical setting, and then get their agreement and randomize them to this.

The main points are that the EERW study has internal validity as long as you account for all of the people randomized to the two groups when you actually conduct the study. If you were to conduct the study twice -- let's say you did the study that's being proposed here, and then you put everybody back on drug, and then you did the study again -- if you actually crossed patients -- in other words took everyone who was maintained on

treatment and put them on placebo, and switched them to treatment, that would be the classic definition of a crossover study. In general, if you were going to do this, though, you could also just simply implement a randomization over the course of observing patients over time to see, over a short period of time, a longer period of time, whether or not the patients who remain in the study, a group of them, maintain some sort of benefit.

So it's a different way of approaching it, but the point is that the EERW study really is an ascertainment of the group of patients who are randomized, to know whether the patients who are randomized to placebo notice that they're being randomized to placebo in some way, shape, or form.

DR. BICKET: Thank you for answering my questions.

DR. BATEMAN: Dr. Farrar, I was just asked by the DFO to have you state your name into the record, if you'd do that, please.

DR. FARRAR: Oh, I'm so sorry. It's

Dr. John Farrar, University of Pennsylvania.

DR. BATEMAN: I'd like to ask the same question I asked Dr. Katz, which is should we be concerned that patients who are doing really well on the treatment during the run-in period will get to the point of randomization and then say I don't want to be randomized with the potential to be titrated down or tapered down to placebo? Is there concern about substantial dropout prior to that randomization point?

DR. FARRAR: There certainly could be some dropout from that perspective, but understanding that the majority of patients who are going to enroll in such a trial, to volunteer for it in any way, will be on opioid, probably on opioid, when they come in. So the fact that they're volunteering for this study means that they're either not happy -- I guess they could just be really wanting to participate in science, but I tend to doubt that -- and that they're unhappy with their therapy in some way, shape, or form. If the study is presented in a reasonable way, to be

honest about it but to also make the point that we're trying to decide what works and what doesn't, they might be very willing to do this.

In the clinical trials that have been done using EERW studies, this has not been a huge issue. There is the issue, though, of potentially putting people back on study drug after the randomization period and basically telling patients that they will be put back on drug. It has the advantage that it avoids people saying, "If I feel really terrible, I'm just going to be left to fly in the wind." It also helps blind the study because patients during the period before are going to have ups and downs, and sometimes pain's worse, sometimes pain's better. If they are randomly assigned in the time that they're switched to placebo, then they don't know when that happens, and if they know, if they get really bad, that they can be asked to be "put back" in quotation marks, on the study drug. It may be of benefit.

Anyway, that was a longer answer, perhaps, than you needed.

DR. BATEMAN: No, that's helpful. Thank you.

Dr. Joniak-Grant?

DR. JONIAK-GRANT: Yes. Thank you.

My question is related to the comment that you made, that the homogeneity of the population reduces generalizability. It's my understanding from going through the briefing documents and such that the response to ER/LA seems more dependent on the individual versus the pain category. If that is the case, does that mean even though there's more a homogenous population, that perhaps the results would be more generalizable, at least across chronic pain conditions, or would you say that that would be taking a big leap?

DR. FARRAR: What I tried to do is to make the point that we are selective of the patients we put on any agent like this, and specific. If we think about it as what happens in clinical practice, I would argue that the patients randomized in the EERW study in fact are the patients that we would be having in clinic, and

therefore it would be generalizable to that patient population. But it requires that they reach an effective therapy within the dose limits, and that is a clinical population, but it would not apply to the people who can't do that, and that's the issue, is it doesn't apply to the entire U.S. population, it applies to a specific population.

DR. JONIAK-GRANT: Thank you.

DR. BATEMAN: Great.

We have time, I think, for one quick question.

Dr. Sprintz?

DR. SPRINTZ: Cool. Hi. This is Michael Sprintz, and, Dr. Farrar, I had one question about the tapering.

Have you considered buprenorphine as a tapering tool or other comfort meds such as clonidine? I know with the elimination of the DATA 2000 waiver, anyone can do that, and that may be a possible solution to the problem of patients knowing whether or not they're being tapered.

DR. FARRAR: Yes. The experience that we've

been looking at in a broad number of EERW studies is that patients getting tapered to placebo works remarkably well, much better than happens in clinical practice because we think that it's blinded, and that there is a use of a rescue during the period. So while, yes, I think that trying to give some other drug might be useful, I'm not sure it's going to help very much. Buprenorphine in particular, as you know, could in fact precipitate some withdrawal symptoms, depending on how it's given to the patient. So there is, I think, an issue related to that as well.

DR. SPRINTZ: But that would be a tapering protocol issue. We use it a lot.

DR. FARRAR: Of course, of course, of course, and I don't disagree with that. I just don't think that it's necessarily going to buy you very much in this study. Also, I'm not at all sure that you would have much success recruiting patients into the study if you said you were going to switch them to buprenorphine, but it depends on the --

(Crosstalk.)

DR. SPRINTZ: Versus tapering off completely.

DR. BATEMAN: Alright --

DR. SPRINTZ: Okay. Thank you.

DR. BATEMAN: Alright. Thank you.

We will now break for lunch. We'll reconvene at 1:00 p.m. Eastern Time.

Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to reconvene around 12:50 p.m. to ensure that you're connected before we reconvene at 1:00 p.m. Thank you.

(Whereupon, at 12:02 p.m., a lunch recess was taken, and meeting resumed at 1:00 p.m.)

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

(1:00 p.m.)

DR. BATEMAN: We will now proceed with the FDA presentations from Dr. Elizabeth Kilgore.

FDA Presentation - Elizabeth Kilgore

DR. KILGORE: Good afternoon. My name is Elizabeth Kilgore. Today, Dr. Roca and I are representing the team from FDA, who have worked to prepare for this meeting. The OPC and Dr. Farrar have already presented many of the pertinent issues for your discussion today; however, in this presentation, I would like to offer additional context on some of these issues. In my presentation, I will cover the purpose for this meeting. Next, a brief description of the scope of the PMR will allow me to define the research question that we seek to address in the study under consideration, and then I'll touch upon how patients currently eligible for long-term opioid therapy and opioid pharmacology make studies in this population challenging.

Throughout our discussions with OPC, three

clinical trial design paradigms were considered. Due to the challenges of opioid pharmacology and the patient population, we do not think any of the designs ideally address the research question; however, the enriched enrollment randomized withdrawal design may offer the best compromise among the designs contemplated. We seek the committee's input on this critical issue today. We also seek the committee's advice regarding specific issues with the EERW protocol under consideration. Last, I will summarize the presentation.

As you've heard, designing and conducting a study to address the PMR has been challenging, to say the least. This process has lasted nearly a decade. The PMR requires holders of NDAs for extended-release, long-acting opioid products to conduct a study to assess the long-term efficacy and risk of opioid-induced hyperalgesia.

We convened this meeting to stimulate a robust scientific discussion around a study design that is most likely to address the objectives of the PMR. While this PMR is limited to ER/LA

opioids, we acknowledge that available data show that safety and efficacy concerns of opioids are not limited to ER/LA products. The focus of this PMR is to assess the long-term efficacy of these products in the context of the serious risk they pose. Given that this PMR was issued nearly 10 years ago, it is also affected by historical artifact.

Before approving any medical product, the agency conducts a thorough benefit-risk assessment of safety and effectiveness. For drugs, absent reasons to act otherwise, the agency has extrapolated findings from replicated 12-week efficacy studies to support long-term effectiveness of a drug product across many indications. Historically for opioids, efficacy has been based on 12-week duration studies; however, studies for different indications may be shorter or longer than 12 weeks to support long-term effectiveness. There are data to suggest that some risk of opioids might be related to longer duration of therapy. Patients on longer term opioids greater than 12 weeks

continue to be at risk for substance-use disorder, overdose, opioid-induced hyperalgesia, and other opioid-related adverse events, so demonstrating that effectiveness is maintained is very important.

Thus, the knowledge gap here is whether opioids retain effectiveness over more than 12 weeks to offset risk over longer periods of time. The public health question to be addressed under this PMR is narrow. Do opioids remain effective for longer than 12 weeks?

The agency's perspective on the study design to fulfill PMR 3033-11 has evolved with experience. An early trial design initially implemented to address the PMR, a randomized withdrawal design without enrichment, has been discussed in detail earlier by OPC. As stated by OPC, this study was terminated due to poor patient accrual.

Since then, three major study designs have been considered. This part of the presentation covers the specific designs considered for this PMR and their advantages and disadvantages from the agency's perspective. Key challenges of trials in

chronic pain have been presented earlier by OPC. These are the challenges that have been considered, and we look forward to your comments on these various aspects of the trial design: comparators, looking at placebo during withdrawal; the population, identifying the appropriate patient population; endpoints, pain intensity is the typical endpoint, but here a novel endpoint is being proposed; and discontinue rate, the issue of dropouts is always a concern in confounding the ability to accurately assess differences in pain between treatment groups.

As has been addressed by the OPC, shown is a diagram of what is generally considered the gold standard clinical study design, the randomized, double-blind, placebo-controlled, fixed-dose parallel group design. Patients are consented and screened, and eligible patients are randomized to, in this case, opioid or placebo.

This is a brief summary of the pros and cons of the placebo-controlled design previously submitted and considered for this PMR. The key

advantage is that if the study population is chosen carefully, there is a minimal chance of unblinding. There are several disadvantages, including possible difficulties recruiting, occurrence of dropout, and whether the placebo group would actually represent low-dose opioid instead of true placebo. Patients with pain that is less severe or do not respond to rescue opioid are likely to drop from the placebo arm, potentially narrowing differences between arms.

The EERW design, diagrammed in a simplimatic form here, has been discussed also in detail by OPC. The study has two key features. It includes an open-label period, reflected by the green arrow, and the double blind, in the blue arrow. In the early part of the study, the population is enriched to limit continuing patients to those who respond to study drug and can tolerate it. Compared to the conventional parallel group study that I just showed, the other feature of this design is late randomization with a short double-blind period, reflected by the blue arrow.

In a one-year study, patients would be on active or comparator for a relatively short period of time. The EERW has been used in other therapeutic areas, including psychiatry and cardiology. For this patient population, the EERW design offers advantages. Patients may find the study appealing because they are guaranteed to receive an adequate dose of opioid. This improves the feasibility of the study. The study is expected to have less dropout than a study with early randomization, which limits confounding due to differential dropout.

The key disadvantages to the EERW design in a study of opioids is the potential for unblinding because patients will become accustomed to the effects of the drug. Also, the enrichment period eliminates patients who don't respond to opioids or cannot tolerate them, which is not reflective of the entire population in need of such an analgesic.

This diagram is nearly identical to that shown four slides ago and does not warrant extensive explanation. The classical

active-controlled parallel group study uses early randomization and with study patients over a one-year period on either opioids or the best non-opioid regimen. As an aside, Dr. Erin Krebs of the Minneapolis VA MC published a study conceptually similar to this in 2018.

In her manuscript, Dr. Krebs reported the results of her 12-month randomized, open label study of opioids versus non-opioid therapy. She enrolled VA patients with moderate-to-severe chronic back pain or pain due to osteoarthritis despite analgesic use. Dr. Krebs conducted her study between June 2013 and December 2016. Due to changes in opioid prescribing practices since then, it might not be possible to conduct a similar study today.

While a high bar, if designed as a superiority trial, this design would provide persuasive evidence of long-term opioid efficacy. As in the placebo-controlled conventional trial design, due to the early randomization, this design also has a relatively low risk of unblinding;

however, given the realities of current opioid prescribing, most eligible patients would expect to be escalated to an opioid and a study with a non-opioid comparator is expected to be difficult to recruit.

Also, given that eligible patients would have failed non-opioid therapy already, over the course of a year, the likelihood of dropout for lack of efficacy in the control arm is high. In the current proposed protocol, NSAIDs may be used as a background therapy, making comparison to NSAIDs problematic.

At this time, I would like to point out specific design issues in the protocol under consideration. To revisit the research question, the agency would like to assess whether opioids remain effective for time periods longer than 3 months. The EERW may represent the best compromise between feasibility and management of dropout. In assessing the EERW protocol currently under review, there are five considerations for discussion that I have listed here. We will be

asking you about these considerations.

As noted earlier, there are data supporting opioid effectiveness for 12 weeks; however, some patients may require opioid therapy for many years. As a practical matter, the OPC and agency have agreed that a one-year period is sufficient to extrapolate efficacy. While conducting a one-year trial in such patients is challenging, dropout in the proposed trial may be mitigated with the proposed time-to-treatment-failure endpoint and use of opioid rescue. Dropout is also mitigated because only patients remaining in run-in are randomized.

The eligible study population has been a compromise between fidelity to current opioid prescribing guidelines and clinical trial feasibility. The pain diagnoses in the inclusion criteria represent some of the most common conditions for which patients are using long-term opioid therapy, and the eligibility criteria require patients to have failed multiple accepted therapies to justify long-term opioid therapy.

However, the patients actually enrolled will be heterogeneous in terms of baseline pain intensity and will not reflect some severe disabling conditions such as complex regional pain syndrome, and may have a variety of confounding comorbidities.

The proposed primary endpoint, as shown, differs from the historical primary endpoint for ER/LA opioids. Historically, the primary endpoint is the difference in pain intensity from baseline to the end of double-blind. In the proposed trial, the primary endpoint represents a time to loss of efficacy or treatment failure.

Note that need for maximum rescue is not part of the composite endpoint. The agency has had internal discussion about the usefulness of an additional component to the composite endpoint, namely use of sustained maximum rescue therapy. We welcome your thoughts about whether it would be appropriate to include it as part of the composite endpoint.

A long-term EERW design conducted in

patients on opioids presents a significant risk of unblinding. Patients will have been on varying doses of opioids for 42 weeks at the time of randomization. They will have become accustomed to the effects of opioids, be they analgesic, psychotropic, or noticeable somatic functions such as bowel habits. The OPC has proposed to use an unblinding questionnaire to address this. COWS and SOWS will also be administered to monitor for opioid withdrawal. The protocol proposes a gradual taper over up to 8 weeks, depending on maintenance dose.

Opioid-induced hyperalgesia components have been presented by OPC. Given that this PMR was established to address a potential long-term risk of opioids, the protocol contains surveillance for the development of OIH. The proposed definition of OIH consists of an element of pain intensity and changes in quantitative sensory testing.

We know that the committee can appreciate the unique challenges in designing and executing a study to inform our public health question. In our

preparation for this meeting, we considered a number of interesting related public health questions; however, at this point, given the knowledge gap in defining the benefit-risk relationship for long-term opioid therapy, we seek to answer a narrow question shown in the first bullet.

As we have shown in our presentation, the EERW may or may not represent the best design compromise; however, the agency and OPC have proceeded to develop an EERW protocol for your consideration today. We welcome your thoughts on this matter.

Thank you for your attention. We're happy to answer questions from the panel now. Please address your questions to Dr. Roca, who will identify the most appropriate FDA respondent.

Clarifying Questions for FDA

DR. BATEMAN: Okay. We'll move on to clarifying questions.

We'll now take clarifying questions for the FDA. Please use the raise-hand icon to indicate

that you have a question and remember to lower your hand by clicking the raise-hand icon after you've 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.

Our first question, Dr. Joniak-Grant, please.

DR. JONIAK-GRANT: Thank you.

Dr. Elizabeth-Joniak Grant.

My question is about the inclusion of looking at the opioid-induced hyperalgesia. Given that the definition is still being figured out with that, and there's no currently validated ways to diagnose or assess, and it sounds like the point of

the study is really to look at long-term efficacy, I'm wondering if someone at FDA could speak more to why this is being included as part of this study, and what could be the potential benefits of including it and the potential pitfalls of including it.

DR. ROCA: Hi. This is Dr. Roca. I'll start out with that, in the context, it is an important piece of information that we think would be helpful. In addition, it is part of the PMR, and that's part of the reason why it is part of the study.

I'm going to ask Dr. Liberatore for a moment to just comment on the issuing of the PMR and why OIH was included in the PMR. Dr. Liberatore is our our deputy director for safety.

Commander Liberatore?

CDR LIBERATORE: Hi. Thanks, Dr. Roca. Yes. So I'm happy to try to answer this.

The postmarketing requirement authority is written such that we must require studies in the context of a safety issue, and the safety issue

that was outlined in 2013 was opioid-induced hyperalgesia. While we're still interested in learning more about that today, the focus of the study is, indeed, as you pointed out, long-term efficacy.

DR. JONIAK-GRANT: But given that there's no sort of valid way, at this point, to assess it, why is it continuing to be included? What are we seeing that would be the benefit of it, and what would be potential misapplications of it?

CDR LIBERATORE: I think I can -- oh, sorry. Dr. Roca, did you want to start first?

DR. ROCA: Sure. I do think that there is information that we can learn from this study, and I think that your comment that there is no way to assess it is true in the context that there isn't a definitive diagnosis, but there are certain ways that were described early this morning as to what could potentially help you evaluate that somebody is experiencing OIH. Now granted, there is no agreed-upon definition, so you're correct that there might be a little bit of potential

disagreement as to whether that is the proper way to do it. However, we do think that this study has the potential to identify that and to provide additional information as well.

One of the things that we can also consider would be whether there are other maneuvers that could be done doing the study itself to try to establish whether the patient has OIH, and those are actually internal discussions that we're having that we will probably discuss also with OPC at some point in the future.

DR. BATEMAN: Thank you.

Dr. Brittain?

DR. BRITTAIN: Yes. This is Erica Brittain. I have sort of a big-picture question, and maybe I've missed it somehow. I'm not exactly clear on what happens if this study is done, and a statistically significant difference is not seen between the arms? So what would be the consequence of failing to detect that difference? It has consequences to me when I think about statistical power.

DR. ROCA: Okay. And you're specifically speaking to efficacy or you're picking up a follow-up question with respect, for example, not being able to pick up anything with respect to OIH? I just want to make sure I understand what you're asking.

DR. BRITTAIN: I'm talking about the main question of efficacy --

DR. ROCA: Efficacy --

DR. BRITTAIN: -- yes, if you don't see a difference in the arms in terms of long-term benefit.

DR. ROCA: Okay. I think that that will be a very important and interesting finding. What we will do with it I am not certain, but I do think that you're correct; that if there is no statistical difference between the two, we'd have to, first of all, try to assess why there wasn't a statistical difference.

As you know, there are many reasons why a particular protocol may not end up meeting its endpoint, or finding -- quote/unquote, "winning,"

or fulfilling the question. So we would need to make sure that we take a look at potential issues, and the overall findings as well, because if there isn't a statistical difference, you're right, that would be a question. However, you could also get some information, even if there isn't statistical difference between the arms, that you could potentially utilize to get a better understanding of the effectiveness. So we would have to really take a look at the results of the study to assess why there wasn't a statistical difference.

DR. BRITTAIN: I guess what I partly was trying to understand is would there be any consequence to the label, to the indication, or would it more be guidelines to prescribers, or what's the goal?

DR. ROCA: Well, I think that that would depend -- going back to the original question, if the results are not statistically significant and there is a reason that we can identify, then one of the things is we would be having to see whether there was anything with the results that would or

would not impact the label, based on the strength of the findings. However, if the results are significant -- and maybe this is on the flip side that you're asking if they're so significant -- there could be implications to the labeling. But that would be if the trial was done properly or well done, and if we could interpret it.

So going back to your original question, if the results are not statistically significant, we need to find out why, and we feel that the results of the study were not interpretable or "real," quote/unquote, then we probably would not be able to do anything with the label.

DR. BRITTAIN: Thank you.

DR. ROCA: Sure.

DR. BATEMAN: Dr. Bicket?

DR. BICKET: Thank you. My name is Mark Bicket at the University of Michigan. My question is related to the key question that was presented; do opioids remain effective for more than 12 weeks? And I was hoping to hear a little bit more

discussion about if the focus of that question is really an evaluation of the benefits and risks of the therapy or if we are primarily concerned with a demonstration of the benefits in the context of just opioid-induced hyperalgesia, because I think that would help clarify a little bit about the trade-offs with the trial designs there. Thank you.

DR. ROCA: I think that definitely you want to see the benefit of continued therapy. The question I think you indicated related to opioid-induced hyperalgesia, that would definitely be one of questions. But also, as you probably noted, with respect to the protocol itself, there are other aspects and other risks of opioid therapy that are also going to be looked at.

So I think it will be one of those things, that you'll be looking at the efficacy in relation to the OIH, as well as to other potential risks as well; not just OIH, but definitely OIH is the focus. I'm not sure I answered your question, though.

DR. BICKET: Yes. I think you were starting to get at this relative importance of the OIH to the other possible risks that would be there, and the viewpoint of the FDA that it is important to know about all these other risks as well, or if the main risks that we're concerned about is OIH and other postmarketing requirements studies have largely addressed some of those other risks that are there.

That would be one viewpoint, or another viewpoint would be, well, OIH is one of the risks that are with an opioid therapy, and we also very much care about some of these other risks that are there, that are quite important in their own right.

DR. ROCA: That's pretty much the second description, that we very much are interested in OIH, but I think we're also interested in the other risks as well, the way you described the second scenario.

DR. BICKET: Thank you.

Dr. Bateman, if you could permit one follow-up question?

DR. BATEMAN: Sure.

DR. BICKET: So my follow-up question is related to a comment you made just a moment ago, Dr. Roca, I believe about some of the labeling. Are there labeling considerations that the committee needs to think about when we're considering the enrolled enrichment randomized withdrawal design versus others, meaning would use of the enrolled enrichment randomized withdrawal design have any implications about what the labeling might be versus one of the other approaches? Thank you.

DR. ROCA: I don't think that the particular design of one versus another would have an impact on the labeling. I think what's really going to come out is what the results are of the trial. Whatever the labeling implications are, it will be what comes out of the trial, whether that is the EERW protocol that we're talking about today or whether that's another design that the committee feels may be more appropriate. It would end up being the results of that particular trial that

would impact labeling. So I do not believe that it would be dependent on the particular design that ends up being finally decided upon.

DR. BICKET: Thank you for answering my questions.

DR. ROCA: Sure.

DR. BATEMAN: Dr. Horrow?

DR. HORROW: Thank you. Jay Horrow, industry representative. This question relates to the interpretation of the trial results.

Dr. Comer in her presentation mentioned the heterogeneity of the population with respect to pain etiologies. Does the FDA, or for that matter, does the sponsor, intend to provide subgroup analyses of the primary endpoint according to pain etiology at enrollment? As part of that question, is there a consideration for stratifying randomization according to pain etiology and/or a desire to cap percentages of enrolled participants according to the pain etiology?

DR. ROCA: This is Dr. Roca again. Sorry. I hadn't introduced myself, for the record, for the

previous responses.

I think you're correct. I think it is important to be able to assess whether the pain differs depending on the etiology, so we'll start out with that premise as to whether that can be best accomplished by stratifying it at entry, or the thing that you proposed, which is to cap certain etiologies. Whether that may be the way to do it can certainly be discussed when the statistical analysis plan comes in.

I think we have certainly been discussing the protocol, as you have heard, but the statistical analysis plan is still pending because a lot of the issues are still needing to be worked out, but we can certainly include what you are proposing with respect to how do you assess difference in response based on etiology. We can certainly include that as part of our discussion because it is a valid point.

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

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 meeting, FDA believes that it's 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 applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant'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 considerations of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals 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 is treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

I will add that each OPH speaker will be given five minutes to speak, so please keep your comments within the five-minute limit.

Speaker number 1, please unmute yourself and turn on your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and

any organizations you are representing, for the record?

DR. ZUCKERMAN: Thank you, and can you put my slides up, please?

(Pause.)

DR. ZUCKERMAN: That's not my slides.

(Pause.)

DR. BATEMAN: Okay. We're going to hold for just a moment while they work on getting the slides up.

DR. ZUCKERMAN: Okay. There we go. Thank you.

I'm Dr. Diana Zuckerman, president of the National Center for Health Research. My comment today will rely on my research experience at Yale and Harvard, and in my current position, and my expertise on FDA policies. Our non-profit think-tank focuses on the safety and effectiveness of medical products, and we do not accept funding from companies that make those products, so we have no conflicts of interest.

What do we know about opioids for chronic

pain? AHRQ analyzed hundreds of studies, and concluded that opioids are associated with quote, "small improvements versus placebo in pain and function, and increased risk of harms, even at short-term follow-up, with evidence on long-term effectiveness very limited, and there is evidence of increased risk of serious harm that appear to be dose-dependent," unquote.

The CDC guidance stated that quote, "Non-opioid therapies are preferred for chronic pain. Clinicians should maximize the use of non-pharmacologic and non-opioid-pharmacologic therapies as appropriate for the patient and specific condition," unquote. And we agree with Commissioner Califf that CDC's 2022 revised guidance concluded that even after all these years, there's still a quote, "paucity of evidence on the potential benefits of long-term opioid use."

The Consortium has provided impressive experts today; however, my perspective and expertise results in different conclusions. Enriched enrollment data will only be relevant to

patients who tolerated and responded well to opioids, and that's been described as a narrow result, and it's the intent of the design, and that's why the results will not inform clinical practice in a way that can improve care for chronic pain patients, and the results will not inform opioid labeling, which is a major goal.

We've heard how difficult it is to enroll pain patients in a randomized study, and any randomized study is going to delay labeling changes. So doesn't it make more sense to change the labels now, based on what we already know?

The study purports to be a one-year randomized trial, but most of the study consists of an open-label study. The taper is too short to prevent terrible withdrawal symptoms for some patients, and the plan to give patients up to 240 milligrams of morphine is too dangerous. Those design issues can be modified, but they add to questions about the quality of the research design, which is fundamentally flawed. It's not really blinded because most patients on placebo will know

that, as will most clinicians conducting the study.

So what will this study tell us? How generalizable will the results be? Unfortunately, not really generalizable. So is it ethical to require patients, who are dependent on opioids, to be given a high dose of morphine, followed by a rapid taper, followed by placebo? In addition to withdrawal, won't that potentially make them even more desperate and more reliant on opioids?

Patients deserve better. We're really concerned that the study being considered has fundamental flaws, and will patients be fully informed of the risks of these studies? Will family members be fully informed? Who would be willing to participate if they were fully informed? Who will benefit from the results of the study?

Number one, I don't think the study could ever be completed because the design is likely to result in too many placebo patients dropping out, but if the study is completed, the results will tell us nothing about the risks and benefits of extended-release long-acting opioids for all

patients with chronic pain. And design being considered seems to favor the status quo since the patients being randomized will have responded well to opioids, and the general population of patients with chronic pain will not be studied.

So the people who manufacture, sell, and prescribe extended-release long-acting opioids are the ones most likely to benefit, not the patients. Thank you for serving on this important advisory committee, and please consider the fundamental changes that would be needed to design a randomized clinical trial that answers the essential questions about which patients are most likely, or least likely, to have benefits that outweigh the risks of these extended-release and long-acting opioids. Thank you for the opportunity to speak today.

DR. BATEMAN: Thank you.

Thank you.

Speaker number 2, please unmute yourself and turn on your webcam. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you're representing, for the

record.

DR. KOLODNY: My name is Dr. Andrew Kolodny. I'm the medical director for the opioid policy research collaborative at Brandeis University. My comments today are on behalf of Physicians for Responsible Opioid Prescribing, an organization that has no relationships with industry. I will disclose that I have personally recently worked on opioid-related matters for the World Health Organization; United States Congress; Department of Justice; state AGs; and the WHO's series Dopesick.

The origin of the postmarketing requirement for this study was the decade-old request from a group of academics, health officials, and clinicians for FDA to better regulate the claims that opioid manufacturers were making. In response to that request, FDA issued postmarketing requirements for opioid makers to get the evidence to back up the claims that they were making.

Since then, we've had an accumulation of observational and clinical evidence that promotion of long-term opioid use as safe and effective for

chronic pain has harmed patients and contributed to a public health crisis. Dr. Califf's press release announcing this meeting also discussed a report. The report that FDA commissioned was on its handling of opioids, and it was a report that was mostly favorable. It was one area where it did criticize FDA, and it was on FDA's reliance of EERW design for opioid approvals. It pointed out that FDA's decision to allow EERW grew out of improper private meetings with drug makers.

There are three fairly obvious problems with EERW design. EERW is not double blind. It's not even single blind. Patients could take a drug with a strong psychoactive effect for weeks and months and switch to a placebo and are likely to know it. They will know how it feels when they take an opioid, and they will know how it feels when they miss a dose and withdrawal begins to set in. And when they experience withdrawal symptoms that are relieved with a rescue dose, they will certainly know that they were given the placebo. EERW design should not be called double-blind.

Number two, for obvious reasons, the results from EERW are not generalizable because only patients who tolerate opioids and find them helpful are randomized. Number three, the placebo group will experience withdrawal-induced pain hypersensitivity, which is an expected opioid withdrawal symptom. And something that we've known for decades is that protracted opioid withdrawal symptoms can last up to 6 months after opioids are discontinued.

It is not an accident that EERW fails to account for this. The reason opioid makers rely on EERW for NDA approvals is that it makes it possible to show that the drug performed better than placebo because of the increased pain sensitivity in the placebo group.

According to a recent review by AHRQ, which was the basis for the CDC guideline, "Evidence of long-term effectiveness is lacking. What we do have is good evidence of harms that are dose-dependent." The CDC has stated that, quote, "The science of opioids for chronic pain is clear.

For the vast majority of patients, the known, serious and, too often, fatal risks far outweigh the unproven and transient benefits." The VA guideline published just a few months ago, its first recommendation, which was issued as a strong recommendation, was, quote, "We recommend against the initiation of opioid therapy for the management of chronic non-cancer pain."

I'd like you to think about it for a moment. This study recruits patients doing poorly on short-acting opioids. Is it ethical to switch these patients to extended-release opioids? If they were not doing well on short-acting, shouldn't they be offered non-opioid approaches rather than higher doses of around-the-clock opioids? Wasn't it the practice of switching patients from IR opioids to ER opioids that got us into this mess in the first place?

Results from an EERW design are not generalizable because the randomized subjects are unique. One of the ways in which they are unique is that the opioid exposure during the open-label

phase will have changed their brains. Placebo-controlled studies have shown that in as little as 30 days of chronic opioid use, there are changes to areas of the brain that mediate impulse control and affect; for example, the right amygdala shrinks. These findings have been confirmed in different labs, and it is not clear that these changes are reversible. These changes may also help explain why after 30 days of continuous use, there's a 40 percent probability that patients will remain on opioids one year later.

Last week, FDA made an incremental change to opioid labels, but the indication is still a multibillion dollar giveaway that allows drug makers to claim that OxyContin and other extended-release opioids are safe and effective for long-term use. When FDA first called for this study in 2013, it was essentially kicking the can down the road. The time for opioid labels to accurately reflect scientific evidence and comply with federal law is long overdue. Thank you.

DR. BATEMAN: Thank you.

Speaker number 3, please unmute and turn on your webcam. Will speaker number 3 begin and introduce yourself? Please state your name and any organization you're representing, for the record.

DR. CONNOLLY: I'm Dr. Nancy Connolly, I'm speaking on my own behalf, and I have no relationships to disclose.

I have never met a person on chronic daily opioids who didn't have chronic pain every day. I don't say that easily. I've been a primary care doctor for over 20 years in both academic and private settings. I'm a specialist in internal medicine, infectious disease, addiction, and integrative medicine. I'm currently a clinical assistant professor at the University of Washington in Seattle.

Pain is an extremely common presenting complaint, and I've treated hundreds, perhaps thousands, of patients over the years for pain, both with and without opioids. I want to briefly share a little of what I've learned over many years in clinical practice.

I created this diagram based on my research and clinical experience to help talk to my colleagues, residents, medical students, and patients about the long-term effects of opioids. Opioids, both long and short-acting, work the same way. They make you feel better. They don't so much eliminate the pain as make you not care about it. They cause some degree of euphoria, analgesia, somnolence, and they slow your gut motility.

That wears off; you feel yucky, depressed, and agitated. Early on, relieving the pain feels good and the withdrawal is not significant. The longer you take the medication, however, the worst the withdrawal, and the more you need to take to relieve the pain and feel better.

A few things I'd like to note. First, regardless of where you are in the curve, when you take the drug, you feel better. Second, the longer the half-life of the drug -- long versus short-acting, methadone versus morphine -- the longer the time between peaks, but there are always ups and down. You will never completely flatten

the curve. Finally, because of tolerance, which is universal, the curve invariably trends downward. Again, I have never, over 20 years in clinical practice, seen a patient on chronic daily opioids who did not also have daily pain.

This is my mother. She suffered her whole life from rheumatoid arthritis. Sorry. She had chronic pain her whole life. For the majority of her life, her quality of life was good. She raised three children on her own. In her 50s, she earned a PhD in psychology and she worked as a licensed therapist until the year before she died.

Remember, she suffered from rheumatoid arthritis. This was many years before she started opioids, this picture. In 2010, she suffered a loss. Her pain was bothering her more, and she went to her PCP for help. She was treated initially with Percocet, and pretty quickly escalated to long-acting opioids. Gradually, her pain began to define her life in a way it hadn't before. She thought they were helping her. She took what she was prescribed, and I watched as her

quality of life declined.

For all that I pleaded with her and with her doctor to get off them, she felt she needed them to function. She developed enumerable problems she never had, stomach problems; mood swings; fatigue; depression; dizziness; pains in places that don't typically affect those with rheumatoid arthritis such as her mouth; and she had repeated falls.

Since the changes were slow and subtle over years, it wasn't until after her death in 2020, when I cleaned out her papers, that I realized just how constrained her life had become, and how much of her creativity and vitality had gone long before her death. She died within a week of a fall on high-dose opioids and in excruciating pain. I believe that chronic opioids took years from the end of her life. Her brother at age 93 is still doing very well. It took richness, vitality, and creativity from the last decade of her life.

During two decades in clinical practice, I have seen this story over and over, patients feeling they need the drug while being blind to how

much of life they've lost and how much pain they continue to have that might have long since passed. I have long had a special interest in chronic pain, and it is a very common scenario in the primary care doctor's office. I once reached out --

DR. BATEMAN: Please complete your comments, please. You're five minutes is up.

DR. CONNOLLY: I'm sorry.

I believe we have enough clinical experience to know that long-acting opioids are neither safe nor effective, and I appreciate the time you're taking in your thoughtful review of these studies. I'm sorry to go over time.

DR. BATEMAN: Thank you.

Speaker number 4, please unmute yourself and turn on your webcam. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you are presenting, for the record.

DR. CALEB: Good afternoon. I'm Caleb Alexander. I'm a pharmacoepidemiologist, an internist, and professor of epidemiology and

medicine at Johns Hopkins. By way of disclosures, I'm former chair of an FDA Peripheral and Central Nervous System Advisory Committee, and I direct an FDA-funded Center of Excellence at Johns Hopkins, and I've served as an expert witness for government plaintiffs in federal and state opioid litigation. My comments are my own that I express today and not necessarily the views of Johns Hopkins.

Despite many shortcomings in the FDA's historic response to the opioid epidemic, the FDA still has incredible opportunities. To be clear, the single most effective thing that the FDA could do to improve opioid safety is to rein in the label of ER/LA products so that it's aligned with clinical evidence. No number of committees, and hearings, and workshops, and white papers, and guidance can take the place of this long overdue action.

I also want to briefly address three remarkably fastidious misconceptions. First, the fact that fentanyl accounts for most opioid deaths doesn't diminish the imperative to improve the

clinical value of prescription opioids. Secondly, there's no inherent conflict between reducing opioid overuse and improving quality of care for those in pain. Third, well-done studies have unequivocally established high levels of addiction and non-medical use among individuals taking opioids for chronic non-cancer pain.

In 2020, my colleagues and I published a review of FDA-approved opioids in the Annals of Internal Medicine. Our key finding was that for more than 20 years, the FDA has approved opioids often in narrowly-defined populations, tolerating the drug, and systematic collection of important safety outcomes has been rare. Any future ER/LA trial should avoid an EERW design. Frankly, it's striking that the agency would even consider such a design in 2023, given that it cherry-picks winners and yields highly uninformative conclusions regarding efficacy, let alone effectiveness.

Despite this, the briefing materials advanced many arguments for the design, some such as that it's consistent with prior approvals raise

the deadly serious question as to whether the FDA is really seeking to change the way it does business regulating these products; others, such as that it minimizes dropout, may be factually true, but come at the expense of yielding critical insights and overlook other well-established methods to handle this problem; yet others, such as that it's unethical to give placebo, presuppose placebo is worse than treatment and that there isn't an active comparator possible, yet just after arguing that placebos may be unethical, it's argued that there's such a large placebo effect that a parallel group study might not show that ER/LA opioids are efficacious. This may be factually true, but it's a telling problem for opioid makers, not the FDA and the public that the FDA serves.

It's also argued that the EERW design is more sensitive than alternatives since other designs include non-responders. The fact that they're non-responders is exactly the point. What's being suggested is to throw them out and see if the product works. Is that the standard we

should be using for this critical postmarketing requirement? In short, these arguments suggest a curious and persistent attachment on the part of the FDA to a statistical design that's completely at odds with the agency's professed commitment to a fresh new approach.

We can all agree that the EERW design answers a different question than a non-enriched prospective design, so I suppose the question is, why more than 20 years into this epidemic, the FDA would risk squandering this valuable moment by examining the persistence of efficacy among a highly select subpopulation, rather than requiring sponsors to demonstrate whether ER/LA opioids work in the first place? Any ER/LA trial should also incorporate other pragmatic elements, ranging from methods of investigator recruitment, to intervention design, to the nature and determination of follow-up and outcomes. The trial should also systematically assess important safety endpoints, including tolerance, nausea, vomiting, as well as non-medical use and diversion.

We all know that the settings in which products are studied for approval differ importantly from those in which they're used in practice -- I mean, that's one of the pearls of the field of pharmacoepidemiology -- but there are few places where this gap has been as wide and with resultant harms as great as when it comes to opioids.

The safety and efficacy information sponsors have provided to gain market access has been incredibly uninformed in understanding the actual safety and effectiveness of these products. This trial represents a tremendous opportunity for the FDA to demonstrate its stated commitment to a new path. As millions of Americans, and I am sure all of you, know all too well, there's not a moment to lose. Thank you for your consideration.

DR. BATEMAN: Thank you.

Speaker number 5, please unmute yourself and turn on your webcam. Speaker number 5, begin and introduce yourself. Please state your name and the organization you are representing, for the record.

MR. THOMPSON: Good afternoon. I am Edwin Thompson, president of Pharmaceutical Manufacturing Research Services. I submitted to the federal docket a document addressed to this committee with the assumption you received my document, and hopefully you have read it. If not, please do so before you make any decisions or vote.

You've been asked to design and recommend a clinical investigation that would provide substantial evidence of efficacy for the use of extended-release opioids in the treatment of chronic pain. As you know, extended-release opioids are contraindicated in the treatment of acute pain. Their use is limited to chronic treatment.

In the preamble of CFR 314.126, it's real clear, the agency's own regulations. The purpose of conducting clinical investigation is to distinguish the effect of the drug from bias, and enriched enrollment randomized withdrawal protocol knowingly, knowingly, introduces bias into the investigation rather than eliminating bias,

violating the purpose of the investigation. This research design artificially inflates the effectiveness of the drug and significantly underestimates the safety of the product.

Democratic Senator Hassan and Republican Senator Braun sent Commissioner Califf a letter in April of 2022, one year in advance of this meeting, expressing their concern for using enriched enrollment randomized withdrawal clinical investigations to assess opioid efficacy. They also asked Commissioner Califf to remove any unsupported efficacy labeling from opioids. They knew a year in advance you would be asked to support this investigation. Their letter is attached to my docket submission. I ask you to read their letter before you vote as well.

Let me show you why your participation in this meeting is so very, very important. This slide reports overdose deaths for prescription opioids -- prescription opioids -- from 1999 to 2021. As you can clearly see, deaths have continued to increase over these 22 years, and

continue to grow as you attend this meeting. If we were to build a memorial to prescription overdose deaths, it would be five times the length of the Vietnam Memorial, and growing. Over these 22 years, there are greater than 280,000 preventable -- preventable -- overdose deaths.

Today, we have a growing prescription opioid epidemic. You can choose to continue it or you can choose to stop it. The source of these overdose deaths are prescriptions from licensed physicians practicing under FDA labeling. Indescribable. Again, you can choose to continue it or stop it.

This meeting is an admission by the FDA that they do not have substantial evidence of efficacy for the use of opioids in the treatment of chronic pain. Unsupported efficacy should be removed from the label, period. These 280,000 prescription overdose deaths require this clinical investigation to have unequivocal magnitude and unequivocal certainty, a standard unachievable by an enriched enrollment randomized withdrawal investigation. Thank you for the opportunity to speak to you.

Thank you.

DR. BATEMAN: Thank you.

Speaker number 6, please unmute yourself and turn on your webcam. Will speaker number 6 begin and introduce yourself? Please state your name and any organization you're representing, for the record.

DR. BALLANTYNE: Good afternoon. I'm Jane Ballantyne. I'm a professor of anesthesiology and pain medicine at the University of Washington Seattle. My views are my own views and not those of the University. I don't have any conflicts of interest as described.

The history does not bear repetition, except to say that the combined extension of opioids to people with chronic pain and to launch into that market of extended-release opioids led to disaster. In no small part, the level of catastrophe was due to the widespread use of a class of drugs indicated only for people who are already opioid tolerant and for use only around the clock.

There are rational safety reasons for these

stipulations by the FDA, but what was unforeseen was that by their very nature and per these stipulations, these drugs would tend to leave their users highly tolerant. High levels of tolerance would compromise both the efficacy and safety of the drugs and would make it hard to discontinue the drugs, even when they were not achieving the desired analgesia. Because the brain is presented with opioids 24 hours a day, continuous usage is highly likely to produce tolerance, and this will worsen over time.

Although there are reports of patients attaining stable analgesia with a stable dose, in practice, dose escalation is more likely. High doses of themselves have many adverse affects, not least of those embraced by the term "pronociception," the worsening instead of improving of pain. The pronociceptive effects of high-dose and high-potency opioids can be experimentally tested and may reverse when doses are reduced.

Clinically, such opioid-induced

pronociception on hyperalgesia is easily demonstratable when skin hypersensitivity develops. The question is, are these demonstrable effects clinically relevant during opioid treatment of chronic pain, and do they worsen the pain that's actually being treated? An added complication; opioid dose escalation, if needed, seems to restore analgesia.

The difficulty determining the clinical relevance of this type of toxicity-induced hypersensitivity resides in the complexity of its underlying mechanisms and the fact that many of the changes overlap with or may be indistinguishable from the hypersensitivity that develops with chronic pain itself. Such changes include receptor upregulation, epigenetic changes, and neuroinflammation, resulting in, for example, increases in the excitatory peptides and increases in endogenous opioid term.

Opioid-induced hyperalgesia is so named partly because it recovers upon removal of the inciting opioid. It can also be, in effect,

overcome by dose increase, and must therefore also be seen as part of the tolerance spectrum. If opioid tolerance began and ended with opioid-induced hyperalgesia, there would be a relatively simple explanation for paradoxical pain; yet the neuroadaptations that arise with continued opioid use are not simply a toxicity effect. Neuroadaptation resulting in multiple forms of tolerance is inevitable with continued opioid use and becomes more embedded over time.

Conditioned intolerance should be mentioned because it's an example of the enduring effect of neuroadaptation. Conditioned tolerance can re-emerge together with its associated drug-specific withdrawal symptoms, even years after drug use has ceased. Linked to conditioned tolerance, tolerance can also be an allostatic adaptation and attempt to achieve homeostasis. Allostatic drug tolerance opposes the drug's effects with drug opposite effects. In the case of opioids, these would include negative emotions and hyperalgesia.

Both emotional and pain affects emerge during drug withdrawal or simply during changes in tolerance. Since the latter can be brought about by multiple factors, including ever-present psychological factors, this type of tolerance and its associated withdrawal must be considered continuous.

Unlike toxicity type pronociception, these types of tolerance are too complex and enigmatic to be testable, yet they are clinically important because they underlie the commonest clinical outcome of prolonged chronic, continuous opioid use. The user is convinced that the opioid is needed because the withdrawal produces intolerable pain. Pain relief is inadequate, yet there's an overriding fear of re-emergent pain.

Multiple clinical studies now support that continuous opioid therapy does not provide useful analgesia and produces serious risks. Tolerance in all its complexities explains why.

DR. BATEMAN: Please wrap up your comment. We're past five minutes.

DR. BALLANTYNE: One component of opioid tolerance is testable at all. The EERW proposed protocol ignores the complexity of tolerance and the enduring nature of neuroadaptations to exogenous opioids. Thank you for your attention.

DR. BATEMAN: Thank you.

Speaker number 7, please unmute and turn on your webcam. Will speaker number 7 begin and introduce yourself? Please state your name and any organization you are representing, for the record.

DR. SULLIVAN: Good afternoon. I'm Dr. Mark Sullivan. Can I have my first slide, please?

I am professor of Psychiatry and Behavioral Sciences at the University of Washington, and adjunct professor of anesthesiology and pain medicine, and adjunct professor of bioethics and humanities. I have 35 years history of treating chronic pain at the University of Washington Pain Center and 20 years of research into opioid therapy for chronic pain. I previously prescribed opioids for chronic pain, although do that no longer other than buprenorphine.

Disclosure, I was hired by the PRC to review their protocol in detail. I will not address details of that that were not discussed in today's meeting because I signed a non-disclosure agreement. I've also been a paid consultant in opioid litigation. I've received no payment for today's presentation. These are my own opinions, not those of the University of Washington. I am going to focus on the phenomenon of opioid dependence because I think that's crucial in understanding efficacy testing for opioid therapy for chronic pain.

I'm going to look at EERW study designs as a way of understanding opioid efficacy, and my argument is that a randomized withdrawal method cannot distinguish long-term opioid efficacy from withdrawal hyperalgesia, which is a well-described phenomenon first noted by Peggy Compton in 2003. Sometimes it's been called withdrawal-associated injury site pain. Launette Rieb in Vancouver has studied this in people who inject drugs, who showed a prevalence of 41 percent. Another study by

Blumenthal in 2020 reported a prevalence of 57 percent. Trial 3033 tries to address this phenomenon of opioid efficacy by studying opioid-induced hyperalgesia.

So that's the way they try to address the hyperalgesia question, but the relationship between opioid-induced hyperalgesia, or OIH, which occurs during exposure to opioids, and withdrawal hyperalgesia, which occurs during withdrawal of opioids, is not known. It's just not been studied. We don't know which signs of OIH predict withdrawal hyperalgesia. There's an evolving literature relevant to this.

A related phenomenon, interdose opioid withdrawal, including muscle and joint pain, has been interpreted to be the return of the original pain problem -- that's the whole idea behind the concept of breakthrough pain -- however, it has been shown to be more closely related to opioid dependence, prescription opioid-use disorder, and depression and anxiety by a number of studies, by Rodriguez-Espinosa and Coloma-Carmona in recent

years. This means that the 3033 trial does not have internal validity and is not a valid trial of the efficacy of long-term opioid therapy, so it's not going to do what it's supposed to do.

Finally, enhanced enrollment creates a highly constrained and artificial study population that does not parallel any known clinical group of patients. This makes it very difficult to know to which patients the 3033 study results would apply. Just because X percent of 3033 study participants show evidence of efficacy, this does not mean that X percent of any discernible patient population will show similar efficacy. 3033 thus will not tell clinicians which patients with chronic pain will respond to long-term opioid therapy.

Briefly, I wanted to put this within a broader study context. Adverse outcomes from tapering long-term opioid therapy have been reported and are currently an active issue in opioid policy debates. They have led to calls to loosen the CDC opioid dosing guidelines, but the problems with opioid taper do not demonstrate that

we should remove or de-emphasize opioid dosing guidance, which will lead to more patients on opioids at higher doses, with more adverse events, including those associated with tapering. We have previously underestimated the complexity of putting patients on long-term opioid therapy; now we are underestimating the complexity of taking them off.

Thank you for your attention to my comments. I appreciate the opportunity to speak.

DR. BATEMAN: Thank you.

Speaker number 8, please unmute yourself and turn on your webcam. Will speaker number 8 begin and introduce yourself? Please state your name and any organization you're representing, for the record.

DR. MAZLOOMDOOST: Hi. My name is Danesh Mazloomdoost. I'm representing myself. Can I please have my slides?

I'm a dual board-certified anesthesiologist and pain specialist trained at Johns Hopkins and MD Anderson, respectively. As a Kentucky native, I returned home to Kentucky because it's one of the

epicenters of the opioid epidemic, and I wanted to develop a multidisciplinary model that effectively treats pain without feeding this epidemic. As the medical director of Wellward, my team and I treat thousands of patients each year, many of whom are opioid naïve and manage effectively without opioid exposure.

For those inherited with chronic opioid therapy, or hereafter called COT, our opioid de-escalation program slowly tapers opioids while simultaneously treating the underlying condition causing pain with our systematic multimodal pain approach. Our average COT patient is managed on less than 20-milligrams morphine equivalents, well below the CDC guidelines and less than half of the MME of all clinics in Kentucky.

Our evidence-based treatment recognizes that opioids have limited long-term efficacy with adverse effects on multiple organ systems. These adverse effects are well documented and go far beyond addiction and overdose. The endogenous opioid system is heavily regulated across many

organ systems, and exogenous opioids cause neuroplastic changes that overwhelm endogenous opioid systems. As a result, many of our inherited COT patients have half a dozen other medications to address these adverse effects, but of greatest concern is the increased pain response because of opioids.

Chronic opioids impact pain processing and evoke a pronociceptive response attributable to changes in DNA expression and intracellular signaling. These alterations are slow to reverse and in many cases irreversible, leading to COT patients having chronically maintained increased sensitivity to pain.

Comparing pain sensitivity between two patients with the same pathology causing pain, this blue line represents undulations of pain in an opioid-naïve patient, and the dotted line representing an average pain experience. An opioid-dependent patient, on the other hand, experiences wider undulations of pain, as represented by this red line, which are far more

difficult to endure or adapt to. Over time, the analgesic effects wane due to tolerance, but the hyperalgesic effects remain, as evidenced by clinical studies of patients with a history of opioid dependency.

Opioids blur the line between organic pain from an underlying condition and the adverse effects of opioids that increase pain volatility. I routinely see opioid-naïve patients thrive, whereas those with the same condition and grade of joint degeneration on COT struggle to get by. If we look at three patient populations with similar conditions causing pain, all three may have similar conditions, but they have radically different pain processing as a result of opioid exposure, with each stage showing diminishing prognosis.

Speakers in favor of EERW posit that identifying the underlying pain generator is not feasible, but it is, and it ought to be the goal of research advancement. Thinking of pain as if that's a disease infers that palliation is equivalent to the treatment of that condition

causing pain, and that's simply not true.

Chronic non-cancer pain is a complex set of many different conditions, and lumping them together without a thorough pathologic differentiation is akin to treating multiple cancers with the same chemotherapy, except in the case of opioids and pain, the pharmacological intervention has a known adverse effect on the curability of the disease. The physiological adaptation to opioids causing hypersensitivity is not an isolated occurrence limited to rare patients; it is a well-documented finding supported by studies and clinical experience.

As someone with significant patient experience in the field, I can attest that opioid de-escalation is a painstaking process. It takes months, if not years, and many patients never fully regain their pre-exposure pain processing capabilities.

The study design of EERW introduces a bias to both arms that presupposes long-term opioid superiority to non-opioid treatments. It confounds

the acute effects of opioids with long-term efficacy. The study design taking opioid allostasis into consideration would be less biased if comparing opioid-naïve patients to those who are escalated and maintained on opioids, similar to the design of the SPACE randomized-controlled trial published in JAMA in 2018 that Dr. Kilgore also referred to.

DR. BATEMAN: Please wrap up your comments. You're out of time.

DR. MAZLOOMDOOST: Thank you.

Titrating opioids and expecting 10 weeks to be sufficient to taper and normalize pain physiology is unethical, given the known prolonged effects of exogenous opioid allostasis. Thank you.

DR. BATEMAN: Thank you.

Speaker number 9, please unmute and turn on your webcam. Will speaker number 9 begin and introduce yourself? Please state your name and any organization you're representing, for the record.

DR. FRANKLIN: Yes. Thank you. Dr. Bateman and distinguished members of the advisory

committee, I'm Gary Franklin, medical director of the Washington State Department of Labor and Industries and research professor in neurology and health services research at the University of Washington. I'm also co-chair of the Washington State Agency Medical Directors Group.

Between 2007 and 2015, in collaboration with several dozen of the most highly regarded academic and clinical pain experts in the state, we produced three opioid-dosing guidelines with an emphasis on dosing guidance and best practices. During this time, Washington unintentional deaths from prescribed opioids fell by almost 60 percent, while national numbers continued to rise. It took bold action to begin to reverse this worst of man-made epidemics.

You could say my colleagues and I were the canaries in the coal mine regarding the opioid epidemic. We reported the first unintentional injury deaths from prescribed opioids in a peer-reviewed journal in 2005. These were 32 injured workers who ended up on long-acting

opioids after drug company and surrogates' falsehoods were spread to practicing providers, and which led to newly permissive state regulations. In Washington State, the 1999 regulatory language was that no doctor would be sanctioned based on any amount of opioids prescribed. With this kind of language, the state medical boards were powerless until these regulations were repealed in 2010.

Our injured workers who died from prescribed opioids were productive citizens in their communities, and most had routine musculoskeletal injuries such as back sprains. Many more workers developed long-term disability attributed, at least in part, to taking opioids. The loss of these productive lives is a vastly underplayed story, but it relates to the 9 million working-age adults who have entered permanent disability systems.

So what exactly is the purpose of this meeting? I am not an expert on FDA regulatory processes, but it has been hard for me to understand why the FDA has approved opioids based on EERW trial designs, which rely on reported pain

scores rather than on improvement in both pain and both pain and function. If pain improves a little but there is no meaningful improvement in function with the risk profile of these drugs, what have you really accomplished? The best available evidence on long-term effectiveness using composite outcomes of meaningful improvement in pain and function does not support the use of opioids for routine chronic pain conditions.

Dr. Hamburg and Sharfstein in 2009, in the New England Journal, described the critical role of the FDA to protect public health by ensuring that drugs are safe and effective for their on-label indications. Dr. Califf has reiterated this overarching mission. You are the guardians of the public's health related to opioids.

Please do not approve the use of an EERW trial design to evaluate long-term efficacy of extended-release opioids. These studies will not inform FDA in its regulatory role, nor will they inform clinical practice, and they will certainly not improve care for millions of Americans who

experience chronic pain. Please, fix the labeling; do not prolong the agony. Thank you very much for your time.

DR. BATEMAN: Thank you.

Speaker number 10, please unmute and turn on your webcam. Will speaker number 10 begin and introduce yourself? Please state your name and any organization you're representing, for the record.

DR. GUPTA: Hi. Good afternoon. My name is Ravi Gupta, and I'm a primary care physician, health policy researcher, and an assistant professor at Johns Hopkins University and the Bloomberg School of Public Health. As part of my clinical practice, I care for patients who suffer from chronic pain, as well as those affected by opioid-use disorder. In my research, I examine FDA regulatory processes, the availability of treatments for opioid-use disorder, as well as the political, social, and commercial underpinnings of the opioid epidemic.

I'm speaking today on behalf of Doctors for America, which is an independent organization with

more than 27,000 physicians in trainees from across the country, addressing access to affordable care, community health and prevention, and health justice and equity. Doctors for America focuses solely on what is best for our patients, not on the business side of medicine, and does not accept any funding from pharmaceutical or medical device companies. As part of Doctors for America, the FDA task force is dedicated to ensuring that therapies approved for use are proven to be clinically beneficial before prescribed.

As we're all well aware, hundreds of thousands of people have succumb to overdose in the opioid epidemic, along with countless families, friends, and communities that have been affected by the epidemic, and as has been well documented, the opioid epidemic began with a promotion in prescription of opioids. The role of different parties, including manufacturers, distributors, pharmacies, prescribers, agencies, and civic organizations, has all been well described in promoting the sale of prescription opioids and

subject to numerous lawsuits and settlements.

The promotion of prescription opioids relied on a number of claims that were unproven. One of those unfounded claims, which has been made repeatedly, is the efficacy of extended-release opioids for the treatment of chronic non-cancer pain. Going back at least as far as 1986, case reports, poorly designed trials, and observational studies were used to buttress the claim that opioids were effective for chronic non-cancer pain. Many of these studies suffered from basic but vital issues: small sample sizes, lack of control groups, lack of blinding, and incomplete data collection. In addition, many of the randomized trials followed patients for short periods, often no more than 3 months, but results were extrapolated far beyond the short period.

Many of these studies also employed an enriched enrollment randomized withdrawal study design, which inherently biases the results towards the treatment arm. And yet, despite the shortcomings of the study design and of these

studies overall, they were used to make the claim that prescription opioids could be effective for chronic non-cancer pain.

The proposed trial would likely not meaningfully inform clinical practice and provide little information about the effectiveness of long-term use of extended-release long-acting opioids for many reasons, including selection bias after the open-label phase, potential unblinding for those randomized to the placebo group, and the issue of withdrawal hyperalgesia among the placebo group, biasing the results towards the treatment arm. Results from an EERW trial would also likely not be generalizable to all patients with chronic pain.

As a primary care physician, I regularly care for patients who suffer from chronic non-cancer pain, many of whom have been taking prescription opioids for a long period of time. I can say unequivocally that it takes frequent vulnerable conversations over a long period of time to build trust in the doctor-patient relationships,

who eventually begin to decrease prescription opioid doses and find safer and more effective alternatives to treat patients' chronic pain. Slow tapers must be balanced with the ensuing withdrawal hyperalgesia that patients experience.

The goal is to always treat the patient's. chronic pain to the extent possible, but prescription opioids have become central to the treatment of chronic non-cancer pain in a way that belies their effectiveness. Thank you for the opportunity to offer comment.

DR. BATEMAN: Okay. 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.

We will now proceed to the charge to the committee from Dr. Roca.

Charge to the Committee - Rigoberto Roca

DR. ROCA: This is Dr. Roca. As I mentioned

at the very beginning of the meeting this morning, what I had hope you to do was to take into account the topics for discussion that we put in the background as you listen to the presentations and as you listen to the comments that were just conveyed.

I can't tell if you have the questions up on the screen. I'm going to assume that you do. I am not going to read them, but I'm going to basically paraphrase them a little bit to help put them into context. I do understand that they will be read in a little bit and to put them into the public record.

We basically have three discussion questions, and the first discussion question is to talk about the advantages and the limitations of the EERW, particularly with respect to assessing the long-term effectiveness, and as you discuss it, also to discuss the advantages and limitations of the placebo-controlled design.

One of the things that was touched upon this morning as well was whether there would be

potentially a sufficient number of patients at the end of the trial to be able to make an adequate assessment, so that would be one of the things that we hope to get your comments on with respect to the first question, and it has a part A to it.

The second question was one where we were focusing on different aspects of the protocol. There were a couple of questions that we had that we had hope, for one, would be serving as points for discussion, to jump off for discussion, that may be things that you have identified yourself and maybe things that we thought we would like your input on.

I am not going to go through them again. Again, I gather that you will go through them one at a time, but I would point out that a couple of them were touched upon this morning; for example, blinding. That was one of the things that came up a couple of times, and we'd be very much interested in your observations regarding the potential for unblinding and the strategies that are being undertaken to try to prevent unblinding. There

were several comments regarding very much interest in that.

In particular, one of the ones that we are interested is actually G, whether it would be advantageous to have patients who are diagnosed with OIH undergo a diagnostic/therapeutic opioid taper during through the trial itself, and it would be interesting to hear your thoughts on that. Basically, number 2 is just a couple of items that we thought would serve as seed [indiscernible] for discussion, but you also may have others that came out from this morning's discussion.

The last question is basically to let us know whether you think of other designs that should be considered in the long-term effect. I think one of the things that I mentioned this morning is we believe that this has the potential to get the data that we need, and we all have acknowledged -- and it was said several times today -- that all protocols have pros and cons and different protocols serve different purposes, et cetera, but we think that this one has potential. But we

certainly are open and welcome any comments you may have regarding other designs that we should consider to achieve the goal that we're trying, which is the assessment of long-term effects.

So with that, I will turn it back to you, Dr. Bateman, and I look forward to your discussions.

Questions to the Committee and Discussion

DR. BATEMAN: Okay. Thank you, Dr. Roca.

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. We'll now proceed with the questions to the committee and panel discussions. 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 of the panel. After reading the question, we'll pause for any questions or comments concerning its wording.

We'll now proceed with our first question, which is a discussion question.

Question number 1, discuss the advantages and limitations of using the enriched enrollment randomized withdrawal, EERW, design to assess long-term effectiveness. Discuss the advantages and limitations of using a placebo-controlled design to assess long-term effectiveness. Include in your discussion the likelihood of maintaining sufficient patients in the randomized treatment period in each of these study designs to ensure an adequate assessment of effectiveness at the end of the double-blind treatment period.

Are there any questions regarding the wording of this discussion question?

(No response.)

DR. BATEMAN: Okay. So if there are no questions or comments regarding the wording of the question, we'll now open the question to discussion. I'd ask the panelists to please turn on your webcams to participate in the conversation, and raise your hands if you'd like to comment on question 1.

Dr. Bicket?

DR. BICKET: This is Mark Bicket Market at the University of Michigan. I appreciate the discussion today from many experts in the field, both during the presentation about the trial protocol from the FDA staff and also from the open panel that we just heard from.

I think in terms of thinking about the enriched enrollment randomized withdrawal study and other studies, I think the comment has been made before that there are trade-offs in all study designs, though the enrichment with the randomized withdrawal study design answers a bit of a different question than some of the other studies that are out there.

When I think about the overall purpose of the studies here, I go back to a bit of the key question that came up as a way to help answer this question, and that was about understanding do opioids remain effective for more than 12 weeks and FDA's response to that question.

The point that was brought up I think in response to a query that I had was that it's

equally important to understand both the benefits and risks of the medication in a long-term fashion. I do have concerns about the enrolled enrichment randomized withdrawal design to fully understand the scope of risks that come up when we think about the use of long-acting opioids over a period of time.

There's a systematic review that was mentioned in some of the reading materials by Furlan that alludes to looking at the enrolled enrichment design as they compare to others, largely concluding, if I'm summarizing correctly, that while efficacy may be demonstrated to be similar in some examples, that side effects are largely underreported.

So I think if I'm trying to come at it from the perspective of generating information that's going to be useful to both patients and clinicians, those are issues that somewhat diminish this role of the enrolled enrichment withdrawal study, and would put me in favor of concern of the other designs, given some of the challenges that they

have out there.

To sum up this comment, I would also say it is important, I think, to think about the study that was done by Erin Krebs in the VA population, not necessarily as an example of one that should be mimicked, but more to show that it is possible to follow a group of patients over 12 months. These are difficult studies to do. I want to make sure that's clear. It's not easy. And whether the FDA decides to move forward with the enrolled enrichment or not, whether it's a parallel more conventional approach or something else, these are not easy studies to do with the recruitment and enrollment, and a lot of attention has to be taken into account there. This goes back to some of the concerns about some of the patients' involvement there.

That being said, it is possible to retain these patients; again, very difficult, but I think it could be done. So for that reason, when I think about the advantages and limitations of the two, I tend to tilt forward a different design than the

enrolled enrichment because I don't think it will give patients that I see in clinic, or clinicians like myself, that benefit there.

When it comes to maintaining sufficient patients in the randomized treatment period, we had comments earlier, I think during the OPC presentation, about dropouts. Dr. Argoff mentioned on one of his slides -- I think it was slide 16 -- that the thinking was that they would start off with -- I think if I'm looking at the data correctly -- 1100 patients, and then would go down to around 300, if I'm seeing that correctly. So largely, only about a third of patients would likely get to the randomized withdrawal event versus a cohort study, where Dr. Katz on slide 40 mentioned losing about half of those patients.

Again, from my perspective, I'd rather lose half and have information at their baseline about whom may be responders versus not, than do the randomized withdrawal period and get this cohort in which we've kind of taken care of these adverse events up to there. Thank you.

DR. BATEMAN: Thank you, Dr. Bicket.

Maybe just to make sure that we're comprehensive in our discussion and giving the FDA all the information they need, we can start by focusing on advantages, and then we'll separately take up limitations.

Do people want to talk about what they see as the advantages of this design? I know several of you just put up your hand, so if you want to wait until we get to limitations, feel free to put your hand down. But can we focus on that point first? What are the advantages of this design?

Dr. Joniak-Grant, please.

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. I think one of the advantages of the design is that it's including a sample that would be the most likely in practice to actually be even considered to try in ER/LA. I like that it goes through these different steps that they have to get to, and not having a lot of success with other approaches before they can even begin to try it.

So I think that that's something that we

should consider because I think that's what goes on in reality in clinical practice. We have to go through a lot of steps first before we get to this point.

DR. BATEMAN: Okay.

Dr. Brittain?

DR. BRITTAIN: I will have a lot of comments as well about limitations, but in terms of the advantage of the proposed design, I think it has a clear interpretation. It may not be the interpretation people are interested in, the question people are interested in. Certainly, we've heard some discussion that it may not be the question of interest, but in terms of answering a question, it can answer -- given that you're a responder through 48 weeks, and whatever the time period is, what happens if you're withdrawn at that point; so it can answer for that population what would happen, and we could also use the time-to-treatment-failure endpoint.

Again, we don't have to worry about dropouts that much. I think it can be a fairly

straightforward answer to that limited question. That's it.

DR. BATEMAN: Okay. Thank you.

Dr. Bicket?

DR. BICKET: Just building on that, I think it does have strong internal validity, so that would be one potential strength as well.

DR. BATEMAN: Other advantages people want to highlight? Dr. Joniak-Grant?

DR. JONIAK-GRANT: I think that it might be more feasible in the sense that there might be more patients who are willing to give it a try based on the fact that they are being promised some sort of treatment. I do have some concerns if we're doing a placebo-controlled study, if it was like, well, you'll either get this or you get nothing. I think we can talk later about does it really have to be that extreme between something and nothing, but I do think the fact that they have an option to try could be more attractive to potential participants.

DR. BATEMAN: Okay.

Dr. Sprintz?

DR. SPRINTZ: Hi. It's Michael Sprintz. I want to be clear that the discussion itself is very, very narrow, so as I'm answering it, I'm answering it based on just the narrowness of the question, and to clarify that we're not being asked about safety; it's just about efficacy. That's important to clarify.

When I compare the advantages of the enriched enrollment, it's definitely better than the placebo in this kind of patient population for all the reasons that were stated above or that people have stated previously. The dropouts are going to be huge. I think there may be better solutions than the EERW, but right now the question that's being asked is specifically the advantages of that as compared to placebo, so that's really the context of my answer for that. It's definitely better than placebo.

DR. BATEMAN: Okay.

Other advantages people want to highlight of this design?

(No response.)

DR. BATEMAN: Okay. Then we can turn to -- Dr. Ness, and then Dr. Bicket.

DR. NESS: Again, just along the line of advantages, I guess what I have been impressed with is this at least parallels what I think of as a lot of the clinical practice that we end up doing because you don't have absolute information about if patients will respond. I appreciate the fact that this is done in this controlled fashion, so you're at least collecting multiple pieces of data along the way but, again, clinical practice can and should be that if you aren't sure if it's really helping, you should take people off of these things and do a taper on these kinds of things. Our problem is that, clinically, whenever we do a taper, it's confused by the fact that they know they're on a taper for these things.

I don't know if this is going to be the perfect way of addressing it, but I do think it is an appropriate attempt to address is it still working, and the context of how we might do that clinically, it's just adding a blinded nature to

it.

DR. BATEMAN: Thank you.

Dr. Bicket, did you have something to add?

DR. BICKET: Dr. Ness did a great job summarizing the comments.

DR. BATEMAN: Okay. Terrific.

Perhaps now we'll move on to limitations, and I have a feeling we're going to have a little more discussion here, so limitations to this design?

Dr. McAuliffe?

DR. McAULIFFE: Well, I'll just step out there, and just talking about the design itself only, not other concerns I have about the study. The burden of participation for patients who enter the study is very, very significant, and the risks of bias and the potential for unblinding patients in the placebo arm during the tapering phase. As people have already commented on, the limitations of generalizability of these findings to other types of pain patients, unless we somehow categorize these patients. These are just a few.

There are many, many limitations to this type of study.

DR. BATEMAN: Thank you.

Dr. Brittain?

DR. BRITTAIN: Yes. I guess it's probably going to be a repeat of what others have said but, again, I took to heart a lot of the comments that were made in the open public hearing about the fact that this study, because it's looking at responders, is it a prime to find a difference once the withdraw occurs? Now that, again, is ok in terms of the context in that population. It's asking a question narrow to that population, but we won't learn much about non-responders.

Now, it is true, to be fair, they do have the open-label period in which something can be learned about the natural history -- well, not natural history, but the history of people on opioids, but of course is not controlled. The other limitation is that it's not clear to me that the blinded phase will be truly blinded, and since the endpoint is subjective, that's obviously a

concern. But I think that will be probably a concern in any study design, but my understanding is that it may be more of a concern in a Withdrawal design.

DR. BATEMAN: Thank you.

Dr. Jowza?

DR. JOWZA: Thank you. What I worry about with the enhanced enrollment study designs -- and I'm seeing them more in opioid studies -- is that you're cherry-picking your respondents, and when you're taking a look at studies that take a look at effectiveness, you're already screening out people who don't find the treatment effective, so you have a biased set of study participants in there.

I kind of worry about the long-term implications of this if we say that this is an ok way to proceed because I'm not sure if the data that we're going on, if you look at effectiveness of medications, actually really hold in the way that we think it does because we're not including people for whom the medication is not effective because they don't make it to the randomization.

The other part of it is, with a randomized withdrawal, what happens is that patients or the participants are on the medicine. And this is an opioid, and I think something that we underplay is that with long-term opioid use, there are changes that take place in the nervous system that are not readily reversible, and I'm talking about just changes outside of what would cause withdrawal sometimes. But what I see is personality changes on top of some of these biological processes that we talk about. What we're assuming is that once the medication is tapered or withdrawn, that those changes no longer are present and, clinically, I don't find that this is the case. So when we talk about randomized withdrawal, and we're taking a look at that to study efficacy, I'm not sure if that's the best way to do it for an opioid study.

DR. BATEMAN: Thank you.

Thank you.

Dr. Horrow?

DR. HORROW: Yes. Thank you. Jay Horrow, industry representative. I believe that the

limitation here depends on the intended indication language, an issue that is largely overlooked by most of the public forum commenters.

If the trial is to underpin an indication effective for chronic pain, then clearly EERW is a severe limitation. On the other hand, if the trial is to underpin indication language along the lines of effective to treat chronic pain in those who respond to initial treatment, then EERW is well designed. So the FDA needs to consider how they're going to use the results of this intended trial to impact and change, if necessary, any indication language.

I'd also like to comment on the issue of unblinding. I find this argument problematic. Critics deny that opioids are effective long term; however, the criticism that EERW cannot be blinded presumes that they do work. So you can't have both if you want to lodge your criticisms; there's one or the other. Take your choice. Thank you. Those are my comments.

DR. BATEMAN: Okay.

Dr. Bicket?

DR. BICKET: Hi. This is Mark Bicket at the University of Michigan. In terms of some disadvantages, I just want to follow up on the taper conversation. It was reassuring to hear some of the thoughts that the duration of opioid isn't thought to result in the need for longer tapering, and that the placebo aspect would likely also support these quick tapers, though I continue to be somewhat reticent to support quick tapers over just a couple weeks for people on high doses of opioids.

I know it is in different context. The FDA already has some language out there from 2019 about the risks of quick tapers, suggesting in people who are dependent or exhibit some degree of tolerance, that these only go about 10 to 25 percent every 2-ish weeks or 2-to-4 weeks, and there are some larger steps in that taper protocol that is listed. For example, going from 180-to-220 morphine equivalents is a step down of about 33 percent.

So they may have data that suggests that this is appropriate and safe in this context, but

that would be one thing that gets to that issue about both experiences that patients have that lead to unblinding as it goes there.

I just wanted to also build on the comments about this discussion about blinding. I do think in the clinical trial language, we're just concerned about some of these changes with placebo leading to the possibility of confounding, especially when it comes to issues that happen about the possibility of changes with the removal of opioids in the body, and some data on withdrawal hyperalgesia that was mentioned before that could go into that consideration of while there may be differences in the pain effects, there may be confounding from other variables, whether it's mood or personality changes that were mentioned before, things like that, that don't just get wrapped up nicely in the pain intensity measure that will be taken into account. Thank you.

DR. BATEMAN: Thank you.

Dr. Brittain?

DR. BRITTAIN: Just to add on to that, to

Dr. Horrow's point that you can't have it both ways on the blinding, I guess I was thinking more the concern with unblinding would be that patient experience, side effects go away, things that are not related directly to efficacy, but that there are other aspects of taking the drug that they notice have changed. That would be the concern. Of course, if they're unblinded because they're doing worse, that's not a problem.

DR. BATEMAN: Dr. Sprintz?

DR. SPRINTZ: Hi. Michael Sprintz. Yes, I've got a couple concerns about the limitations.

The first thing, as we're talking about the blinding part, I do agree. One of the things that bothered me was when we're talking about the taper and utilizing something that would actually help with the blinding, using something like either a comfort medication like clonidine, or lofexidine, or buprenorphine, or something like that, that would actually manage any opioid withdrawal symptoms.

The fact that it was dismissed is not

consistent with what my clinical experience has been, and granted, that's just my clinical experience. A lot of the patients that we do taper down from opioids do struggle with that, and at the very least, they have an increase in their experience of pain. And that's an important thing to remember, too, is that pain is truly an experience; it's not just physical. It's physical, it's emotional, it's all that.

The other thing I was thinking about when we're talking about opioid-induced hyperalgesia, when we think about the blinding part, for those who might have OIH, those patients should theoretically do better as we taper them off. I don't know if that was going to be something that was actually even being measured during the tapering phase, but how do we manage OIH? Well, you decrease the opioids and they get better. That was one thing that I don't think had been mentioned yet. That's all. Thank you.

DR. BATEMAN: Thank you.

Dr. Shoben?

DR. SHOBEN: Sure. This is a relatively minor limitation, but I don't think it's been brought up yet, and it might fit better in question 2, this idea of who is actually going to stay in this study in order to be randomized to potentially be withdrawn. I know you brought this up during the earlier part of the meeting, Dr. Bateman.

These are patients who are naïve to long-acting opioids, and if they're doing well and think they're doing well, I really have concerns about seeing the same level of participation in this randomized phase we saw in the earlier studies, where they're being randomized to withdrawal sooner and there's really no data there, so I see this potential limitation as this generalizability as are we really going to have more patients in the randomized phase with this kind of design? Thank you.

DR. BATEMAN: Thank you.

Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you. Elizabeth

Joniak-Grant. One thing I was wondering for the panel to think about is that we've talked a little bit about what questions are we trying to answer with this study, and that can really impact whether or not we think that this EERW approach is the right way to go. Would people be more comfortable with this design if all the data was kept and analyzed for those who didn't make it to the open-label treatment phase? So everyone who had said, nope, they're having side effects or it's not being effective, would that be a bit of a compromise in a sense, for lack of a better word, to consider.

DR. BATEMAN: Thank you.

Dr. Brittain, I'll go to you in just a second, but I want to make sure that we're addressing what I think was a recurrent theme in the open public comments, and that was that the design really biases towards the treatment arm. One of the considerations people put out there was the potential for withdrawal hyperalgesia and how that could bias in favor of the treatment arm. We

heard concerns about unblinding, and unblinding for factors potentially unrelated to the analgesic efficacy but withdrawal symptoms or mood symptoms, as people have mentioned. I just want to make sure we get a handle on that and give good feedback on that point.

So I'll go to you, Dr. Brittain, but if others could be thinking about those issues, or if there are other things that came up in the open public comment that you think are important for us to weigh in on, please do so.

Dr. Brittain, and then we'll go to Dr. Ness.

DR. BRITTAIN: Yes. I just want to make a quick comment. I think my understanding of the sample size issue, basically part A here for this design, is that they would continue to study patients until they randomize the number of patients they want. It's not like they're going to set the sample size for the open-label phase and then see how many end up in randomization, that they will make sure they get 400.

Now, maybe it won't be feasible if everybody

says, "No, I'm feeling great. Why do I want to do this?" So it may be a feasibility issue, but at least in terms of this setup, there shouldn't be any reason why they can't get to their number.

DR. BATEMAN: Okay.

Dr. Ness?

DR. NESS: I just wanted to reiterate what Dr. Horrow had said in the sense that the key limitation of this is, this is not going to tell us how everyone who is in pain, how and why they should be using these pain medicines, which was the main concerns we had with this open public forum, was this generalization that this information will be generalized to everyone in pain.

I'm reading this and having the interpretation that this may identify a specific subset of patients who benefit from opioids on a long-term basis. It becomes then a separate policy decision of do you keep allowing these things to be available or validating their availability just for a subset of patients? And that's not the question we're being asked here; that's a regulatory kind of

question. But I do actually think, as long as you maintain those limitations that are present in this EERW study, you may or may not identify a group of patients that do seem to benefit from long-term, and stop there with any of the other sorts of things that go into that equation.

I do think that that's a valuable piece of information to work with because I as a clinician struggle with the ethical sorts of things, as I don't want to deny a therapy, but if I get good evidence that it's really not helping people, which is what this kind of thing could show, then I wouldn't be using it.

DR. BATEMAN: And maybe there's a separate study that's needed to address the broader question.

DR. NESS: Yes. This is only going to address is there a subset of people who might be benefiting?

DR. BATEMAN: Yes. And again, I'd really love people to just weigh in on this question of -- even these considerations aside about the

narrowness of the question being addressed -- is their bias inherent in the design that favors the treatment arm? There are a number of design approaches that have been taken to try to mitigate that, but are they adequate?

Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you. I wanted to speak to what you'd mentioned, talking about the unblinding concern. I think that we also have to be realistic that it's a lot of conjecture in terms of when we taper people off. Are they going to know? Are they not going to be aware? Dr. Ness had mentioned earlier maybe doing a 2-week initial of no tapering because sometimes people automatically think they're being tapered even when they're not.

I would like to suggest maybe we have to think about having the COWS and the SOWS being done before tapering. Chronic pain patients, I'm one, we're complicated. We usually have all kinds of symptoms going on from all the different treatments and all different kinds of medications and things.

I mean, the reality of it is, I took the opioid withdrawal test yesterday when I was reading through things, and I am moderate opioid withdrawal. I haven't taken opioids for years and years and years.

So we have to be aware, too, that sometimes the stuff that we think is so clear-cut, oftentimes we don't know, and we have to sometimes get in there and see what's going on. So I think we can try and assume and guess, but it really at a certain point becomes conjecture as to how much this is going to -- patients are going to be aware that they're receiving placebo.

DR. BATEMAN: Thank you.

Dr. Britain, and then we'll go to Dr. Horrow.

DR. BRITTAIN: Dr. Bateman was asking about the bias question. I guess it goes back to what other people said; what question do you want to answer? If you're answering the question, the narrower question of, within a group of responders, is there truly long-term benefit, I don't think

there's bias. If you think that generalizes to everybody, yes, then there is bias. It really depends on the question.

DR. BATEMAN: Okay.

Dr. Horrow?

DR. HORROW: Jay Horrow, industry representative. Dr. Britain said it very well. I don't need to repeat that.

A question for the agency related to this is -- in particular, Dr. Farrar's presentation and other presentations, including that from the agency -- there was discussion about making sure that the taper start time was a randomized event in time; that is, not everyone's tapered at the same time.

My reading of the protocol did not leave me with a strong sense that, in fact, this was one of the features of the protocol, and perhaps the sponsor and the agency should consider making sure that the taper start time was done in a somewhat randomized fashion in order to minimize the potential for unblinding.

DR. BATEMAN: So maybe can you say a little bit more about that? Why is it important to have a variation in the time that patients are randomized to tapering versus not?

DR. HORROW: Yes. I don't think it's my job to re-present what was already shown, but the experts who did present material indicated that by randomizing the start time of the taper, there was less of a chance for unblinding. We want to minimize that, so we should do it.

DR. BATEMAN: Okay.

Dr. Bicket?

DR. BICKET: Thank you. This is Mark Bicket. I just want to open that conversation. It was Dr. Farrar who had mentioned about this possibility of randomizing the start time. I was just going to echo that comment, and then also say, if the thought is to move forward with the tapering, we've suggested before about possibly expanding the taper period. That could bump it back in terms of the timing of it to prevent more time for tapering, for more gradual tapering doses,

if there's data to, again, support that.

The other thing would be to standardize some of the withdrawal approaches for patients who exhibit withdrawal symptoms during the taper phase. There are non-opioid medications that can alleviate symptoms, some of which had FDA approvals, so there could be a way to incorporate those in a standardized fashion to then permit that to be a possible outcome in addition to the COWS or other opioid withdrawal scores. That may be one option to think about in terms of having available to both arms such that it, again, continues to minimize this issue about unblinding. Thank you.

DR. BATEMAN: Great. Thanks.

Dr. McCann?

DR. McCANN: Hi. Mary Ellen McCann. My concern -- and I'm not sure this is the question that you're actually asking -- is that the study appears -- and I think almost everybody on the committee agrees -- that it's going to answer a very narrow question, and if you accept that, then the study's actually well designed. But the next

step is how do you manage that answer? How do you not confuse the public or not confuse clinicians that there's just a very narrow question answered, and that the broader question has not really been dealt with? And I don't know if that's question number 2 or this question, but that's certainly a concern that I have.

DR. BATEMAN: Interpretation, yes.

Dr. Jowza?

DR. JOWZA: Hi. Maryam Jowza. I just want to be clear on this. When we're talking about the narrow question that the study answers, I'm not sure that we're all thinking of the same narrow question. Is it, in a group of responders to opioids, does a taper cause a 30 percent increase in pain or initiation of a new medication? I just would like to hear from others what that narrow question is to you.

DR. BATEMAN: Okay. Do some of the panelists want to respond to that? What would be the interpretation of the findings?

Dr. Horrow?

DR. HORROW: I see it as a question of definition of the population. It is the population that is being narrowed rather than the question. If we assume that the measures that are proposed reflect long-term efficacy, then the difference between this particular design, the EERW design, and, say, the design that was used previously -- which could use the same endpoint that you just articulated -- the difference would be the population.

An original study which failed because it was not feasible attempted to answer the long-term efficacy question in the general population. This EERW study can answer the long-term efficacy question in a much smaller population; that is, only those participants who have demonstrated that they respond in a tolerable fashion to opioids. That's how I see it.

DR. BATEMAN: Okay.

Dr. Sprintz?

DR. SPRINTZ: Hi. Michael Sprintz. I guess one of the questions that I actually have is, are

these questions that we're answering, or the discussion that we're having, related specifically to an intended indication versus -- as I understand it, this is a clinical study that was required by the FDA that started 10 years ago, so I don't know. Will this result in a change in indications or where are we going with that?

DR. BATEMAN: Okay. I think Dr. Roca wants to respond to that question.

DR. ROCA: Yes. I'm not sure that it needs a change in indication per se; it might. But there are two things that I want to address. One of them is, I was listening to the conversation, and I appreciate that you're trying to figure out is this a narrow question, is this a general question, et cetera.

The question is narrow, and I think some of you have picked up on that what we would like to see is, if patients who are staying on and seeming to respond to opioid therapy, and they tolerate it, are they really responding or not? We don't know if there's long-term efficacy in these patients who

seem to be responders; however, by getting some of this information, we want to know if they're still responding.

Now, there isn't any new indication per se, but if the information of this trial comes out and says, "No, they really didn't respond. Those who you thought were responding were no longer responding," I can envision that that may end up being put into the label to inform clinicians about this. Whether it will change the indication, I don't think so, but it depends on the results. But I can easily see that the results of the trial may yield useful information that should be put in the lead for you guys to be able to see what that means.

So I hope that that helps a little bit, particularly with respect to the question of whether we're trying to answer from the general population. Somebody just walks into the office; will they respond? You're correct. This study is not going to address that patient population.

Does that help?

DR. SPRINTZ: Yes. Thank you very much.

DR. BATEMAN: Okay. Thank you.

Let's talk a little bit about enrollment criteria. During the open public hearing, again, we heard some concerns expressed about the approach of selecting patients who are doing poorly on immediate-release opioids and putting them on extended-release long-acting opioids.

Do people have thoughts about that? And maybe along with that, people can comment on the etiologies of pain that are included, if that's appropriate.

(No response.)

DR. BATEMAN: We're still speaking to question 1. I didn't see these listed in question 2, so I wanted to just touch on that before we move on.

Dr. Sprintz, and then Dr. Joniak-Grant.

DR. SPRINTZ: Again, this is Michael Sprintz.

Dr. Bateman, in regards to your question about if someone's not doing well on

immediate-release opioids, depending on the dosing, and depending on their their pain condition, and depending on other issues there, it's variable, but the probability of them doing better on a long-acting opioid to a significant degree, I'm finding challenging.

That would be my opinion on that one. If they're not doing great on short-acting, the real question is why, and that can be a multitude of answers. There may be some who would do better because of the long acting, but then the primary question is why are you not doing well on immediate-release opioids, and how would that actually be solved by a long acting? And there are too many variables for me to answer more clearly than that.

DR. BATEMAN: Okay. Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thanks. Yes, I agree with that. The phrase was used quite a bit with the short-acting, quote/unquote, "not responded to," and I kept wondering what does that mean; not responded to enough, didn't respond to at all;

contraindications, obviously if they're contraindicated to take them? I wasn't sure if they were contraindicated for those why they would be able to then take the ER/LAs, so I did have some definite questions around that.

I also wanted to ask the panel, because this is definitely not my area of expertise, what they think about the categories that were chosen to be included. The diagnoses, do you feel that those are reasonable categories? They're not representative, but maybe closer to as they could be. The reason I wonder about this is there was quite a bit of saying that, really, response to opioid treatment, and especially extended-release treatment -- often they were saying it says more about individuals; it's more about individuals than the pain category. So I wanted to hear the panel's thoughts about the choices of the categories.

DR. BATEMAN: Yes. Maybe along with that, I think there was a suggestion by one or more of the panelists about capping the numbers enrolled from certain etiologies so there was some distribution

and having pre-planned analyses of subgroups by etiology.

Dr. Zaafran?

DR. ZAAFRAN: Yes. Sherif Zaafran, Texas. Actually, what Dr. Sprintz said, what Michael said, probably, to me, had the most impact, is just a multitude of variability and what the response would look like beyond just etiology.

As we all know, with pain, there's an emotional/behavioral component that is added onto the iatrogenic component and the etiology of the pain component, and that response and how a patient responds, there are so many different variables that it would be almost impossible to parse out, especially in this small population.

Even looking at the different etiologies of the pain really wouldn't answer the behavioral and the emotional component, which may be different from one single patient to another, or from one patient at one time to another, and that really would be difficult to parse out. And trying to make a judgment based on that in this short period

of time I think would be impossible.

DR. BATEMAN: Thank you.

Dr. Bicket, and then we'll go to Dr. Jowza.

DR. BICKET: Hi. This is Mark Bicket. As I understood it, for the patients to come into the study, they would have to have these pain scores between 5 and 9 that would then need to respond, in some fashion, to the introduction in the open-label phase. These pain scores between 5 and 9 sound clinically reasonable. Certainly, if people are on immediate-release opioids and their pain is still in that number, would long acting be a consideration? Certainly, in some patients that could be the case.

I do want to bring up a comment that somewhat relates to that as it ties into the primary outcome, and I think that is the focus on the pain intensity. Often in chronic pain settings, we do care about people's pain numbers, but we also shift away from that a much broader and more functional assessment of how they're doing. We've seen this in some other trials that have

focused on function as a primary outcome or given it that importance.

I know it did come up in the discussion today, and as much as perhaps it would be helpful to, I do think there's some consideration because there certainly are some patients where maybe their numbers may not change that much, but their function may improve, or vice versa; their numbers may improve, but their function actually gets worse. These are some of the difficulties I think with patient populations inherent to that do come into play, I think, when trying to adequately design a study, no matter what design we choose, and just wanted to make sure that that was brought up and some consideration there. Thank you.

DR. BATEMAN: Thank you.

Dr. Jowza?

DR. JOWZA: Lucky mistake. I didn't unmute. Maryam Jowza. Thanks.

On the topic of the patients for enrollment with the specific pain diagnoses -- and I'm glad you brought it up -- something that jumped out at

me is painful peripheral neuropathy being part of the inclusion criteria, because I feel like, overall, clinically in pain, we've moved away from using opioids, or long-acting opioids, especially for chronic neuropathic pain conditions. And the reason for that is, over time, the thought is that it makes it worse, be it the opioid-induced hyperalgesia, tolerance, you name it. It struck me that that was part of the inclusion criteria.

DR. BATEMAN: So do you question whether that should be included, whether neuropathic pain should be one of the indications?

DR. JOWZA: I do. I do. But I also feel, to be fair, while on the one hand a sense is that this type of trial design biases you more towards people who are going to do well with the opioids, on the other hand, if you add this condition, my instinct is that there's not going to be a big difference between those on opioids -- or actually maybe even a worse outcome for those on opioids versus those not on opioids. I would not put that in there.

DR. BATEMAN: Alright.

Dr. Ness?

DR. NESS: Yes. This is Tim Ness at UAB. I had the same thing. When I first saw this set of diagnoses that they were mixing a whole bunch of neuropathic and other things, I guess I took comfort in the sense of looking at the methodology they talked about and doing the subanalyses related to predictors of response because, again, we have a lot of clinical lore, we've got a lot of different sorts of statements that we have about what works and what doesn't work, and we have our own experiences. I was actually hopeful that this information then might help me; that is, it might actually give me real data to say, well, in this prospective process, we couldn't get good pain control in those people, and that was a predictor of response.

That said, I'm not sure we're powered sufficiently to answer all of those questions because we're talking that this is the open-label part of it that's going to give some of that

information; how many people just fail to ever achieve adequate pain control with those diagnoses? I still see some of this information as it would be useful to me in my clinical practice. If I can say that only 20 percent of that group is going to do it and 80 percent of that group is going to do it, I would like that information. I'm not a statistician to tell you if we're powered enough to do that in these subgroups.

DR. BATEMAN: Okay.

Dr. Horrow?

DR. HORROW: Well, since Dr. Ness raised the issue, this was an issue that I had flagged in my review of the protocol. I estimate somewhere in the neighborhood of 25 or 30 predictor variables, based on the list that was indicated in the protocol for this analysis, and I'm fairly confident that that's too many, and it's going to result in spurious designation of variables that are having an impact on the end.

I defer to the statisticians on the panel to comment on the wisdom of including so many

variables in the predictor. I believe that the number of events is hardly going to justify some of the rules of thumb, such as the Rule of 15, in determining that, and I share Dr. Ness' concern about that analysis.

DR. BATEMAN: Okay.

Other thoughts? So maybe we'll wrap up this question by just talking about part A. Include in your discussion the likelihood of maintaining sufficient patients in the randomized treatment period in each of these study designs to ensure an adequate assessment of effectiveness at the end of the double-blind treatment period.

So this is getting to the question of, I guess, dropouts. Do people want to comment on that?

Dr. Brittain?

DR. BRITTAIN: I think I mentioned this before. It seems like the EERW, at least in theory, you can make sure you have enough patients in the randomized portion. It might take a while to get there, but you can do that. We haven't

really talked about the placebo study that's in this question.

DR. BATEMAN: So there you're talking about the dropout before randomization.

DR. BRITTAIN: Yes.

DR. BATEMAN: Okay.

DR. BRITTAIN: So with the placebo design, I think it would be much more challenging.

DR. BATEMAN: Okay. So if we were entertaining a different design, then the issues of dropouts would be more problematic. Okay.

Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you. Elizabeth Joniak-Grant. I think this would have some decent likelihood of enrolling patients and maintaining them. There's a great deal of stigma about using opioids now. There's a great deal of stigma with chronic pain. In my patient communities, there are a lot of people that won't even try them, even when they're suggested. So I think by working with a group that's already at least tried short-acting, short-term ones and short-acting ones, it might be

easier to get them into trying and being willing to participate in this study.

I think we do talk a lot about opioids and things, but we have to be careful not to talk about opioids in 2012 and 2013, and also recognize that today, there are lots of patients who have been on long-term opioid therapy who want to stay on it, and there's a lot of people who don't ever want to start it no matter what the doctors tell them. So I think this does help with that.

DR. BATEMAN: Okay.

What about the issue of dropout after randomization? Maybe after Dr. Bicket's comment, people can comment on that issue.

Dr. Bicket?

DR. BICKET: This is Mark Bicket at the University of Michigan. Part of it I think depends on the information that might be gleaned from the dropouts and some construct of the primary outcome related a little bit. We heard from the OPC members about the thought about this primary outcome that was kind of like a time to an event,

which had advantages thinking about trying to minimize some of the issues about censoring that happens with the survival analysis that's there. That, in theory, could be applied in other contexts to try to mitigate some of those issues outside of the enrolled enrichment randomized withdrawal design, as well.

I do think, just stepping back for a moment, the issue about the dropouts comes back to where will that information loss be helpful. It, again, gets back to this key question that the FDA wanted us to address about evaluating this effectiveness of the long-acting opioids.

I kind of go back to this idea that having the dropouts in a cohort would be slightly better. Again, we have variable estimates from the members of the panel today. Is it going to be half the people? Is it going to be less or more based on the 12 weeks studies? It's difficult to estimate, but it would be a notable proportion there. That being said, if people did enroll, you would have baseline information and be able to tell risk

factors for people who did drop out, where data would not necessarily be that informative about them, so thank you.

DR. BATEMAN: Dr. Ness, and then Dr. Brittain.

DR. NESS: Just to reiterate a statement I had made before, because there are significant expectations in what typically is a fairly hypervigilant population who is now having to do a lot of reassessment and a daily assessment of how they're doing, I think unless you have, again, a randomized start to the thing -- so there's a period of time that they know they're definitely on the meds but they're having to report all of these things -- I think you're going to drop people out because they're going to be sure they're on the taper.

That's why, again, a run-in period where you theoretically, after the first 2 weeks, can tell them, "Well, you know, you've still been getting it," that becomes a separate question of things, but they can assess what was due to just their

expectations as opposed to what is due to their actual changing of medications. So I think if you just start right into a taper, I think you're going to have a much higher dropout just because people think they're tapering.

DR. BATEMAN: So doing some setting of expectations at the time of randomization might help you retain patients better in that post-randomization period.

Okay. Dr. Brittain?

DR. BRITTAIN: This is Erica Brittain. Well, certainly the previous comment is concerning. I guess I still would think this design should do pretty well in the sense that the endpoint incorporates doing poorly, as opposed to a pain endpoint at 10 weeks. The randomization period is just 10 weeks, so I would hope most of the dropout will be incorporated into that failure endpoint. And also because it's a time-to-event endpoint, the other dropout can be considered non-informative censoring, but the devil's in the details.

DR. BATEMAN: Okay.

Dr. Joniak-Grant?

(No response.)

DR. BATEMAN: You're on mute.

DR. JONIAK-GRANT: Sorry about that. I almost made it through.

I don't think there will be a huge dropout. It is a shorter period of time. As most people with chronic pain know, sometimes you can't even get in to see your physician for 4 months, even though you're in a crisis mode, so 2 months is very much in the realm of what we experience and what we're told is a very reasonable amount of time. I think it will be impacted by how that taper is handled, which I know we're discussing later under question number 2, so I think we need to spend some time on that.

I think one thing I just want to mention also, as has been pointed to, is having pain patients hyperfocused on every symptom that they're having in their pain can increase pain reports. Having to keep daily logs and daily this, I know for me, sometimes it's much better to say are you

having a good week, or having a decent month? Things like that are part of how you survive and get through having the pain. So it's great that they want to do all these assessments, but we also need to balance that with how much we're going to be stacking the deck a little bit against people noticing everything that could possibly be wrong with their body.

DR. BATEMAN: Okay. Thank you.

Any final comments on question 1? Otherwise, I'm going to briefly summarize, and then we'll take a break before turning to questions 2 and 3.

Dr. Brittain?

DR. BRITTAIN: I just wanted to say we haven't really talked about the placebo-controlled design, which is part of the question. I don't know if there's much to add. I guess I would say, in theory, it's a great design. It just seems like from everything we've heard today, that it would be very hard to keep people in the study for that long. I guess the final question is we could

perhaps talk about variation on that theme, but I just thought since it's in the --

DR. BATEMAN: Yes. No, thanks for highlighting that.

DR. BRITTAIN: -- question, maybe we could talk about it.

DR. BATEMAN: Yes --

DR. BRITTAIN: It's a perfect design if you could somehow make it happen.

DR. BATEMAN: Right.

DR. BRITTAIN: You could even build in this other design as part of it.

DR. BATEMAN: Anyone else want to comment on this. I guess placebo, particularly in this context of the EERW design, are there alternatives that would be relevant?

Dr. Bicket?

DR. BICKET: This is Mark Bicket, University of Michigan. I think it's a great question, and it underscores a lot of the difficulty in terms of constructing trials to ensure sufficient recruitment and retention here. The proposal we

heard today is from a very esteemed group of folks about this enrolled enrichment randomized withdrawal design.

I do agree that there are a number of issues that come to retention with the placebo that's there. Whether you're thinking of one group that only gets placebo versus another that doesn't, in terms of you both had titration-up period, monitoring over periods of time, and then down, versus trying to include some within-person to crossover, they certainly do introduce challenges about increasing the length of the study and/or complexity that make it certainly more challenging while trying to address some of these issues that we're speaking about.

Again, I think fundamentally, they do address different questions. I think it is worthwhile to say that if it is the intent to really focus on individuals who have both gone through an exposure to long-acting and extended-release opioids, and then successfully been on it, and the FDA's main question is, well,

how did these people do when they come off of it, then this enrolled enrichment randomized withdrawal design does a great job of trying to answer that question; whereas I think the clinical community may be thinking that there's a need for a different kind of evidence that's out there that then points us back towards trying to deal with these problems about the challenges that come up with placebo, more traditional parallel group studies, whether they include crossover or not with them. Thanks.

DR. BATEMAN: Thank you.

Okay. I'm going to try to summarize our conversation. I think we covered a lot of ground, and there were a lot of great points that were made, a really rich discussion.

Dividing it first into advantages, I think people articulated -- the panelists articulated -- that the principal advantage of this design is that it is feasible, which is not the case for many designs that we might consider; that it's likely that patients will be able to be enrolled in the trial, and they'll be able to be

retained until the point of randomization.

The study design addresses a clinically relevant question, albeit potentially a narrow one, which is, of those patients who respond to opioids and for whom opioids have some efficacy over the run-in period, what is the impact of withdrawing treatment, and is continuing on ER/LA opioids beneficial in terms of efficacy?

The study design has internal validity and, again, will give us information on a question, albeit perhaps not the main question of relevance, in a general sense of who will benefit from long-term opioid therapy.

The limitations are, I guess, closely aligned with that, in that it's not addressing the broader question of who is likely to respond at the population level and what proportion of the population is likely to respond in a sustained way. We talked a lot about some of the concerns around blinding. I think there was some variation in thoughts about whether that's problematic and whether the withdrawal of treatment and the use of

placebo might bias towards the treatment arm due to withdrawal hyperalgesia or blinding. Some people made the point that if the patients recognize that their analgesic effect is going away, there's no other way to get at the question of efficacy.

We talked a bit about the enrollment criteria, and I think there were some concerns about the heterogeneity of the population, particularly the inclusion of patients with neuropathic pain. Some suggestions included the potential for capping certain indications and planning analyses of subsets of patients to see if there's variation in effect based on the underlying indication.

We talked a bit about this question about dropout. I think the feeling was dropout prior to randomization is something that can be controlled, or you can enroll an adequate number of patients to ensure that you got enough patients to the randomization point. Then dropout after randomization, there was some discussion about the importance of setting expectations so the study is

able to retain patients through the post-randomization period. There was also some discussion about the importance of how dropouts are handled in that the endpoint should incorporate capturing patients that drop out because they're doing poorly, and those that drop out for other reasons could be handled in a non-informative censoring type of approach, so that is something that could be handled in the statistical analysis plan.

Did I capture the main points? Anything else that people want to highlight?

(No response.)

DR. BATEMAN: Okay.

So in that case, we'll take a quick 10-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break. We will reconvene at, let's see, 3:50.

(Whereupon, at 3:39 p.m., a recess was taken, and meeting resumed at 3:50 p.m.)

DR. BATEMAN: Okay. We'll get started again

and move on to question 2.

The question is, discuss the proposed protocol for PMR 3033-11. Include in your discussion the following: is 42-to-52 weeks an adequate duration to assess the long-term effectiveness of opioids;

B, what degree of dropout is expected in a study in this patient population? Will enough patients be expected to complete the study in order for the results to be interpretable?

C, is the time-to-treatment-failure endpoint informative? If yes, should the use of rescue above a prespecified threshold be added as a treatment failure criterion?

D, given the pain scores could be variable, are there measures that could be employed to assure that the threshold for increase in pain is clinically meaningful and does not represent short-term variability?

E, does the proposed tapering scheme adequately mitigate concerns about unblinding?

F, is the proposed definition of

opioid-induced hyperalgesia and surveillance for the development of the condition appropriate?

G, to better characterize opioid-induced hyperalgesia should patients diagnosed with OIH undergo a diagnostic/therapeutic opioid taper?

So a bunch of things to cover here, some of which we've touched on in the previous discussion, but before we start, are there any clarifying questions about the wording or what's being asked for here?

Dr. Bicket?

DR. BICKET: Hi. This is Mark Bicket. Would the group or FDA prefer us to limit our discussions strictly to the enrolled enrichment randomized withdrawal protocol just as presented, or would you also find it informative if we compared some of these elements to the other trial? I just wanted to make sure the next part of the discussion is as informative as possible. Thank you.

DR. BATEMAN: In part 3, we're going to have an opportunity to talk about other designs, so I'd

suggest we focus on the proposed protocol for this discussion question, and then in question 3, we can expand the discussion to other potential designs.

Dr. Joniak-Grant?

(No response.)

DR. BATEMAN: You're on mute.

DR. JONIAK-GRANT: Sorry. It's getting later in the day. For this part, can we go through them one by one versus just --

DR. BATEMAN: Yes.

DR. JONIAK-GRANT: Oh, great.

DR. BATEMAN: We'll go one by one. I just want to make sure we're clear on the questions --

(Crosstalk.)

DR. JONIAK-GRANT: I had to ask that.

DR. BATEMAN: -- and then we'll take them up one by one.

Okay. So if there aren't any questions, let's jump in and start with A, is 42-to-52 weeks an adequate duration to assess the long-term effectiveness of opioids?

Dr. Ness?

DR. NESS: I clicked the wrong button. Sorry. Yes, in a very unscientific fashion, I would agree that this is an adequate duration only because, clinically, if patients have been stabilized out by 6 months or so, they don't seem to ever stabilize out. That's just my clinical experience. Take it for what that's worth but, for me, that would seem to be an adequate duration that I would feel comfortable continuing it.

DR. BATEMAN: Dr. Brittain?

DR. BRITTAIN: Actually, I really have a question here about A, which is, I don't know if they're also asking is 10 weeks enough during the randomized phase, and I don't have a good answer to that because it sounded like some people would take 8 weeks to be fully tapered, and that's part of their 10-week period, and I'm really asking the experts here if they think 10 weeks is enough to see a difference, if there is one.

DR. BATEMAN: Maybe we should take this into parts then. So the first part, is the run-in period long enough to establish that people are

responding and get them on stable dosing, and then the second part can be, is the duration of taper adequate?

DR. BRITTAIN: Okay.

DR. BATEMAN: Dr. Bicket?

DR. BICKET: This is Mark Bicket at the University of Michigan. So the first part of the question about the stable tapering, I agree with Dr. Ness that the time period that's allowed in the current proposal protocol is sufficient to let that happen. This open-label period certainly exceeds what I would anticipate may be needed to help people get to stable dosing. Individuals at the highest dose may need that amount of time to get up to that, and I think it's 260, maybe, as the maximum dose there, which is on the higher side, though there may be some patients who end up getting up to that in this protocol, so that would be sufficient. Thank you.

DR. BATEMAN: Okay.

Any other comments particularly from folks who practice pain medicine? Does 42-to-52 weeks

seem reasonable?

Dr. Sprintz?

DR. SPRINTZ: Yes. This is Michael Sprintz. If you're stabilized out and doing well after 42 weeks, 42 to 52, generally, that's great that you've got someone who's on a stable dose. So yes, from a pain medicine perspective, I would say yes.

DR. BATEMAN: Okay.

Then maybe we'll move to the second part that Dr. Brittain suggested, is the tapering period that's proposed adequate? Is it too short, too long?

Dr. Sprintz, did you want to finish your --

DR. SPRINTZ: Yes. I actually think the tapering is not adequate. I think it's too short. Perhaps other people have different experiences than I've had with a number of patients, but I think that we're going to get -- especially with patients in this group are patients where no other treatment was effective for them, and that's the reason why they're here, so now we're going to taper them rapidly.

I have not seen a lot of success with this group of patients that are requiring opioids for which nothing else has been adequate prior, and then they're going to be on it for a long time, and then we're going to taper them off really quickly, I think it's way too short, or we're not utilizing enough other comfort medications to avoid the withdrawal problem.

DR. BATEMAN: Okay.

Dr. Joniak, and then we'll go to Dr. Brittain.

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. I find the taper to be too quick, especially because there are going to be some patients. that really struggle with it. When I was looking through the charts in the appendix, I think it was on page 5, some of these drops were 15 percent for a week; others were 50 percent for a week. And I was wondering what the rationale was for these really big divisions.

It seemed like it was more about this is a convenient dose going from 150 to 100. It was

going from nice numbers to nice numbers, and really taking into account how much proportionally things were going down. So that was a definite concern I have, especially because -- I don't know. I've been on enough medications where they said, "Oh, you can come off of this super fast; there's nothing," and then you get discontinuation syndrome or something else, and it's a real struggle.

So I think if they want to try to keep it shorter, there has to be something in there to deal with patients who are not doing well with being tapered so quickly, who may be really struggling with it.

DR. BATEMAN: Okay.

It would be great for others to weigh in, too, and if you do think it's too short, perhaps propose alternative approaches.

Dr. Brittain?

DR. BRITTAIN: So again, I'm still asking a somewhat different question -- maybe that's part 3 of this -- which is, is this period long enough for -- because this is the period in which the

primary endpoint will be assessed, and if the tapering is 1-to-8 weeks and the endpoint is assessed by 10 weeks, is that enough time to look at the treatment effect? Again, it may be a separate question than the tapering itself. But I don't know. I'm asking the committee.

DR. BATEMAN: Okay.

We'll go to Dr. Ness, and then Dr. Jowza.

DR. NESS: Just to express the simple opinion, this seems a little fast for coming down if you're wanting to avoid significant symptoms, particularly if they are on the high end of the doses. Part of this is, there's a difference between being in the study and in doing things in clinical practice because you tend to work things at a 2-to-4 week interval when you're doing things clinically, so the tapers end up being much slower. But even then, they seem to get significance, and if you're worried about unblinding, this just seems a little fast.

DR. BATEMAN: And what would you propose as an alternative approach?

DR. NESS: Yes. Well, that's the problem. I haven't found good guidance. I would actually say probably the addiction literature might have a better sense for detox, what they end up using, so those would be the people I would ask about how do you minimize symptomatology with withdrawal.

I, again, work at about half this speed and half the speed that they were using. So it would make it that instead of a 10-week, we're now pushing 20 weeks, and that lengthens this trial.

DR. BATEMAN: Dr. Jowza, and then Dr. Sprintz.

DR. JOWZA: This is Maryam Jowza. I've seen so much variability with respect to how well patients can tolerate a week. Obviously, those on higher doses will require a longer period of time, but I've also had patients who I've tapered down from, say like, 150 MMEs, I've brought them down to 40, and then somewhere they get stuck in that 20-to-40 range where they just have severe withdrawal symptoms, and I don't really quite understand why. So I think adding a little bit

more variability to that 10-week period would probably be better.

But to Dr. Brittain's question, which I think is an excellent one, is that 10-week period enough for you to be able to determine a difference between the two groups because that's really the meat of the study; isn't it? That's what we're doing. That's what this is all there for, and I'm not sure if it is.

I think maybe extending it so that you have the group tapered off and stable would be a better approach; and making it more flexible and not a hard-and-fast 10-week period would probably give you a more fair sense of how people do off of it, so that you don't have issues of withdrawal added in.

DR. BATEMAN: Okay.

Dr. Sprintz?

DR. SPRINTZ: Hi. Michael Sprintz. To comment back on Dr. Ness, my background is actually in addiction medicine as well as chronic pain management, so I've done a lot of, both, tapers and

dealt with chronic pain patients. What we've found in the tapers is normally when I'm transitioning someone off of an opioid, or a traditional full mu agonist, something like oxycodone, hydrocodone, we'll often use either buprenorphine, or clonidine if for some some reason they're not a candidate necessarily for buprenorphine. But I don't use buprenorphine the way I believe that a lot of it has been marketed, which has been traditionally like, "Oh, you just keep them on it forever." No, I actually would do it as a taper.

What we found was that a 15-day taper was a little bit short, but a 30-day taper usually worked pretty darn well. And that way, again, it eliminates the whole withdrawal question, and I think we would get a better result in determining was there effectiveness of the original long-acting opioid because we're not also trying to gauge is this withdrawal-related pain or is it not. I think that the traditional way of just cutting patients down, I think that it's going to confound things.

DR. BATEMAN: Okay.

Dr. Joniak-Grant?

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. I think Dr. Sprintz raises a really good point because I think we do want to try and balance how long this potential placebo period is with getting the information that we actually want. So I think that in terms of keeping people in the study, enrolling people in the study -- they might have fears of being tapered -- saying that some things will be provided would be useful, and then controlling for some of the confounding variables by utilizing buprenorphine could be a big benefit.

Another thing I did want to mention with this, kind of preventing unblinding that we need to think about in terms of safety, how will it be handled -- I'm thinking of a patient who starts going possibly through withdrawal, is having severe symptoms, and going to the ER. They don't know what part of the study they're in. They don't know what's going on. How is that going to be managed?

ER visits, if they have an accident, if they end up having to go to the hospital for something,

how is the information going to get to the treating providers about what's really going on? Because this is a year in someone's life, so a lot of things are going to happen. Are they going to travel or are they going to do different things?

So we have to be mindful, too, that this is a massive amount of time. There's going to be graduations, and weddings, and things, and you're not just going to have a patient that's sitting at home all the time. There are going to be times where they live some life.

DR. BATEMAN: Okay, fair point.

Any final comments on part A before we move on? My summary would be that I think the consensus is that 42-to-52 weeks, or 42 weeks, as a run-in period is adequate, but there is some concern that the duration of taper may be a bit too rapid, particularly for patients that are on higher opioids, and that should really be thought through quite carefully as the protocol's finalized, and that there should be consultation with addiction specialists and others who might be able to weigh

in on whether that period is too brief.

I think there's also some concern that perhaps a longer follow-up period after the opioids are tapered off is needed to fully assess once all of the potential withdrawal symptoms are behind the patient, that would be the period where you'd really want to make the assessment, not during the period of rapid fall off in their opioid doses.

Anything to add to that before we move on to B?

(No response.)

DR. BATEMAN: Okay. We've touched on part B in our other discussion, but we can see if people have additional points they want to make. What degree of dropout is expected in this patient population? Will enough patients be expected to complete the study in order for the results to be interpretable? Again, we, I think, largely covered this topic, but anything that folks want to add from our prior discussion?

(No response.)

DR. BATEMAN: I think the discussion from

question 1 was that while there would be some dropout with adequate enrollment, you could get enough subjects to the point of randomization, and after randomization, the dropout could inform the primary endpoint if it's because the patient's not doing well so that that could be incorporated into the endpoint being assessed.

Part C, is the time-to-treatment-failure endpoint informative? If yes, should the use of rescue above a prespecified threshold be added as a treatment failure criterion? If no, why not?

Thoughts on question C. Dr. Ness?

DR. NESS: Tim Ness, UAB. Yes, the time to treatment failure, I had just a comment. They talked about initiating new therapies would be one of the causes of loss of therapy or time to treatment failure. This is a separate thought, but what about sudden advancement of existent therapy, as in they're already on some medications, and then they escalate that, or as was mentioned, they go to the ER, or they go to other sorts of things? I think those contingencies need to be included.

I do think time-to-treatment-failure endpoint is informative, but I think we need to have some definitions of when did they fail that are a little bit more expanded than what we currently have.

DR. BATEMAN: Thank you.

Dr. Bicket?

DR. BICKET: This is Mark Bicket. Building on those comments, I do think the 30 percent increase in worse pain intensity over 7 days is reasonable, as are these other two. The other contingency that comes up in my mind is we've set for the index chronic pain condition and we are thinking of the trials, proposing to include patients who may have overlapping pain conditions or other pain diagnoses as well. Having one pain diagnosis often puts someone at risk for having others, and fully understanding if one pain medication is for an index condition versus something else may kind of blur those lines a bit and would also want to be handled a bit less.

Some patients either would be started on

pharmacologic therapy that could be construed that way versus others who may not necessarily have those exposures, or certain patients may end up meeting the endpoint versus not in a differential manner, and that could be of concern, so I just bring that up. Thank you.

DR. BATEMAN: Thank you.

Dr. Joniak-Grant?

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. Thank you. I think that for the rescue analgesic, that should be included, but the threshold obviously needs to be flushed out. Are we talking about frequency? What do they mean by that?

Then in terms of worse pain, Dr. Bicket had mentioned that 7 days seems sufficient. I would push back on that a little bit. I think with chronic pain, it's very easy to have a terrible week because you try to travel somewhere, or you try to go to an event, or even just a stressful period in life. So I would suggest that maybe we try to lengthen that to at least 14 days. I don't know what others think about that, but 7 days seems

really a very short period of time for me to say that this means the whole treatment has failed.

DR. BATEMAN: Okay.

Dr. Bicket?

DR. BICKET: Slightly separate comments about the time-to-treatment-failure endpoint. We've heard discussions earlier today that this would be statistically powerful and informative. I do think it is somewhat challenging to interpret clinically and what is a clinically meaningful difference. Statistically there could be a difference found; for example, does a 1-week difference in this composite endpoint matter both to us clinically and to patients versus others?

That's one of the challenges, I think, that comes up with both taking a composite endpoint, so we have these three different markers right now, and potentially thinking about the fourth one with rescue above prespecified threshold. There are challenges for patients to interpret that as well in what is meaningful to them. That kind of shifts some of the trade-offs that we have, so I just want

to be cognizant about that because I'm not sure what would represent a clinically meaningful endpoint there. I do think that including the rescue above a specified threshold would be appropriate as well, and would be in favor of that.

DR. BATEMAN: Yes, because if you go above a certain threshold, you're essentially having the patient be on a high dose of opioids.

Dr. Brittain?

DR. BRITTAIN: Yes, just a quick comment. I don't know if it would be helpful, but I'm hearing people thinking it would be hard to understand a time to event. Of course we use it in lots of disease areas. I don't know if it's any easier to think of it as, at 10 weeks or whatever, the entry is going to be the randomization; what proportion of the placebo group failed and what proportion of the treated group failed. You can use a Kaplan-Meier approach so at that time point, that has all the advantages of dealing with missing data the way the full-time-to-event approach does. I mean, you could still do the main analysis as time

to event, but phrase it in terms of success rates at the 10-week mark. I don't know if that makes it easier to understand.

DR. BATEMAN: A more intuitive approach while preserving the power of the time to event, but giving results in a more intuitive fashion.

DR. BRITTAIN: Yes.

DR. BATEMAN: Okay. Other comments on this? Dr. Bicket?

DR. BICKET: Last comment for me on this. I just want to revisit my thoughts earlier on the shift from pain intensity to the importance of pain interference in these populations; that after a year's point in time, the pain numbers may be less meaningful than actually how their function is doing, and this primary endpoint is still largely pain intensity focused. I just want to put that there. Thanks.

DR. BATEMAN: Alright. Any final thoughts on part C before we move on?

(No response.)

DR. BATEMAN: So to summarize it, I'd say

that the committee feels that the time-to-treatment-failure endpoint is a reasonable analytic approach, although not particularly an intuitive one. Dr. Brittain had some nice suggestions about how you could preserve the power of a time-to-event analysis but present the results in a way that would be more, perhaps, clinically meaningful or intuitive to the people interpreting the data.

Then I think also the sentiment was that the use of rescue above a prespecified threshold, should be part of the treatment failure criterion because if what we're trying to capture is does chronic opioid therapy confer benefit in this population of responders, if you're essentially in the placebo arm reintroducing opioids at a high enough level, that represents a failure of the placebo treatment.

Okay. Moving on to part D, given that pain scores could be variable, are there measures that could be employed to assure that the threshold for increase in pain is clinically meaningful and does

not represent short-term variability?

We've heard a few comments already on this point. Do people want to expand on those or offer other thoughts?

Dr. Joniak-Grant, and then Dr. Ness.

DR. JONIAK-GRANT: Thank you. Elizabeth Joniak-Grant. I think one thing that could be added to this to help to give more insight is there's that patient personal assessment, but they do it at the very end to say what do you think that you were on? I think perhaps when we're talking about they're seemingly a failure, to have the patients not just check off their primary. There was a box where you said, pick one; pick one reason. I think maybe having them actually ask them and do a bit of a qualitative, short write-up of what they see is happening would be really helpful and important, and there's ways to make this reliable. I'm a qualitative researcher. There's plenty of ways to do this that is still good for science and all those things.

I think also the other part is including the

function. I think that's really important because if people sometimes are doing more, their pain levels might increase, so having that be there I think is really important. I was also wondering what the panel thought; I just wanted to bring this up.

They're talking about using one physical function scale across all the different diagnoses instead of the more accurate ones for specific conditions, and are people comfortable with that if we're going to be talking more about including functions, the indices of function, as an important measurement.

DR. BATEMAN: Yes. I think it'd be great to hear from some of the pain researchers about potential instruments for measuring functional outcomes.

Dr. Ness?

DR. NESS: Dr. Ness, UAB. Well, along that line, I favored tests that, at least in our studies, we did with interstitial cystitis. I was associated with the NIDDK's MAPS studies and some

of the other previous trials they did. Actually, a global response assessment, GRA, which is a 7-point Likert scale -- are you much better, a little bit better, not better, it's a ranking all the way down to much worse -- actually proved to be the most valuable piece of information regarding response to therapy that they had because the pain scores always seem to migrate back towards the mean or the starting point. And clinically, we have the same thing; that patients will say, "Oh, they're giving me a 10 out of 10 on their score." "But are you better?" "Oh, I'm so much better." There's a disconnect there that happens, and the global response assessment is one of those things that helps dissect that information out.

I would hope that they would include because right now their mean assessment are things like the Pain Profile Questionnaire, and there's an assessment about the investigator agrees that patients have meaningful improvement. That's one of our criteria. This is just something to put a number on it, and it's a tool that's commonly used.

DR. BATEMAN: Okay. Thank you for that.

Other comments on this question?

So we heard before that 7 days may be a little bit too brief a period to make an assessment. There was some previous concern voiced about that. Any other points people want to make?

Dr. Bicket?

DR. BICKET: I want to respond -- this is Mark Bicket -- to the question about the trade-off between maybe a global function scale versus individual ones. There is a bit of an issue with thinking about assessment burden. There are a number of assessments in the trial. Would it be that much more to add on those individual ones? Given everything else, perhaps not.

My sense is it looked like from the schedule of activities that there's the BPI, which has a functional component to it, and it's fairly well validated across a variety of pain conditions, so that would likely be adequate. I'm kind of blanking because they included another one from a a PROMIS measure or another function there. But the

PGIC, which is somewhat I think to what Dr. Ness was mentioning about, did appear in the open label in the double-blind phase, but I do agree it would be helpful to more integrate that with some of these ideas about what's clinically meaningful.

In some of our other clinical trials, I think we found that it's not too burdensome to include that on a fairly frequent basis with individuals, doing those more daily or granular assessments with those brief questions that would be there. Thank you.

DR. BATEMAN: Perfect.

Any other comments before we move on?

(No response.)

DR. BATEMAN: Okay.

To summarize, I think in previous discussion, there were concerns raised about the 7-day period being too brief and that it could just reflect variability associated with life events and not necessarily changes associated with the treatment. Then there was also, I think, voiced, desire to incorporate functional measures, and the

GRA was suggested. There were some others that were suggested, along with potentially disease-specific measures for the patients.

Okay. Let's move on to E, does the proposed tapering scheme adequately mitigate concerns about unblinding? This is also something we've touched on in the earlier discussion. Does anyone want to add additional comments about this issue?

Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you. Elizabeth Joniak-Grant. Just a quick point. I think we've covered this territory pretty well, but I do think that it's important that when the study is done, they said they'll send information to the healthcare provider. I think they need to tell the patients as well at that point, because it is their information. It's difficult to find care, and they should be aware of what worked for them and didn't work for them. I think that would increase retention and enrollment as well, to know that that information would be given to them.

DR. BATEMAN: Okay. Terrific.

Let's take the last two points together. They're both about opioid-induced hyperalgesia. Is the proposed definition and surveillance for the development of the condition appropriate? And then second, to better characterize OIH, should patients diagnosed with OIH undergo a diagnostic/therapeutic opioid taper?

Can some of our pain specialists on the committee weigh in? Dr. Jowza?

DR. JOWZA: I'll start. Maryam Jowza from UNC. I love the definition of opioid-induced hyperalgesia, the way they defined it. I like the fact that they have some objective tests, which will help with the diagnostic process. We're always told, and under the impression, and clinically have found that an opioid taper does help; it's the treatment of choice for opioid-induced hyperalgesia. So yes, a taper would be good.

DR. BATEMAN: Okay.

Dr. Ness?

DR. NESS: Tim Ness, UAB. I agree with that

completely. Again, they gave a good rationale for how they're going to measure the opioid-induced hyperalgesia. I have my own opinions about adding other modalities, but they made a good enough argument for that. And yes, I think it's standard of care that if you identify this hyperalgesia, you should try to give them a taper to see if they do better off.

DR. BATEMAN: Okay. Thank you.

Dr. Bicket?

DR. BICKET: This is Mark Bicket. I do agree with the comments about the definition of OIH, given its quite variable out there, I think the approach that Dr. Angst and others have taken to create the definition and think about the testing, and the use of the heat modalities, including I think the suggestion by one of our panelists about perhaps including the cold water pressor test to that additional battery there, may be helpful, and then the surveillance time points all appear appropriate.

From a clinical experience, I do know there

is a bit of opioid-induced hyperalgesia that is quite prominent and pronounced in a very small number of patients, and that may differ clinically from the appearance of hyperalgesia in perhaps a subclinical way that may be picked up through some of the testing and maybe some of these slight increases in pain scores that may be seen. So maybe some consideration about how those two different events may be handled; or one is clearly almost like an adverse event of such severe nature, the patient may require hospital admission, which I've certainly had experience treating some patients who've had that happen, and they needed a help taper, in contrast to others where it it may be documented, displayed, and seen there, but not something that is quite as pronounced, and then may need to be handled differently. So I would just introduce that issue that could happen. Thank you.

DR. BATEMAN: Thank you.

Dr. Sprintz?

DR. SPRINTZ: Hi. I'm Michael Sprintz. Yes, I would say the definition's great. Everyone

else had covered that. I would say -- should patients diagnosed with OIH undergo diagnostic/therapeutic opioid taper -- assuming that they do the taper according to the protocol they currently have, that's going to happen.

What I think that they should do is during the taper phase, if you're not addressing any opioid withdrawal symptoms, meaning that they're just doing a decreased taper, then during the taper period, the patients who have OIH, they should be assessing them for, "Hey, how is your pain? Are you getting better?" Because if their pain's improving, at that point, you've done it. But if they do decide to do the tapering in a way that utilizes either comfort meds or buprenorphine, then in those situations, I actually would -- in theory, once you're done with the taper, they should be improved from where they were, so I think it's already being done. We just need to make sure that we're tracking it and monitoring it. But bottom line is, yes, you should. You should definitely do it.

DR. BATEMAN: Okay.

Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you. Elizabeth Joniak-Grant. I'm in the minority here, I think. I find the definition a bit vague. It feels like it has a lot of overlap with different pain conditions. I wonder how it would be separated out from the withdrawal effects, emergent fibromyalgia, other variables at play.

I'm concerned that the validity of QST and other ways of diagnosing it have not been proven, but what I'm most concerned about is how this is going to be used in practice. The results would be written in a very particular way, but we have definitely seen in the past where clinicians kind of run with information that gets put out there in a really fast direction.

I'm thinking about, for example, in the headache space, for a time medication overuse, headache was seen as like the end-all-be-all with treatment, and I know a number of patients, myself included, were taken off things, and it was

insisted, and it basically destabilized our care, and now we've been trying and trying to get back to where we were before we tried it.

So I just get a little bit concerned with how much it does happen. It seems to be rare, but that we don't fill the cart too much and present it as though, oh, this has all been -- yes, this is a great way to do it, this is a great way to determine it, and in the real world having clinicians just run as though this correlation is causation and this is where it's at. So I think we need to be mindful about that and what happens to patients.

DR. BATEMAN: Okay. Well, thank you for that.

Any final comments on part 7-G before we move on?

(No response.)

DR. BATEMAN: I think, in general, people are comfortable with the opioid-induced hyperalgesia definition, although there wasn't universal consensus on that. I think people also

expressed that patients generally should undergo a diagnostic or therapeutic opioid paper when diagnosed with this condition, which is in line with the protocol, so it would be happening anyway.

Alright. I think Dr. Roca wanted to make a comment before we move on to question 3.

DR. ROCA: Yes. Thank you.

My comment is going to be to sort of segue into question 3, where we're actually asking you for potential other designs that you might think would be useful. But before we go there, what I wanted to do is to ask you -- because I think this will be very, very helpful for us -- to actually go and ask each of the panel members whether they feel that the current design, the EERW, the protocol that we're talking about, is fit for purpose to answer the question that we're posing.

That question is whether patients who appear to be responding to opioids are actually truly getting a benefit or not, or is the design so confounded, either by hyperalgesia, or other reasons, things you have heard during the open

public hearing, et cetera, so that the results could potentially be non-interpretable or non-informative? I think, in essence, it's sort of like a summary assessment of what each panel member thinks of whether this proposed protocol is fit for purpose.

I think that that would be very, very helpful if you could actually go around and ask each of them, and then, obviously, you can segue into question 3, which talks about other potential designs that you think would be useful.

Would that be possible?

DR. BATEMAN: Sure. We could absolutely do that. Your recommendation is we do that now before we take on question 3? I think that makes sense.

DR. ROCA: Yes, it envelops it all nicely. You've talked about pros and cons, issues, concerns, et cetera, so now it would be kind of nice to get your overall assessment of whether you think this protocol is fit for purpose or not.

DR. BATEMAN: Okay.

DR. ROCA: Thank you.

DR. BATEMAN: Thank you.

I have the roster in front of me. I'm just going to run through the roster. I think we'll almost treat this like a voting question, if people can respond to Dr. Roca's query, is this protocol fit for purpose? And again, I think that the question being posed is for patients who are responders and are reporting benefit from opioid therapy during the run-in, and are the opioids conferring benefit?

Is that a fair summary of the clinical question, Dr. Roca?

(Pause.)

DR. ROCA: I was trying to find my mute button. Yes, but I certainly wouldn't call it a voting question.

DR. BATEMAN: Okay.

DR. ROCA: Yes, it's more like a summary assessment of their impression of the protocol, because we've had a very nice discussion with lots of different issues, lots of different points, and different variables brought in, and they're all

important, I think. You guys are giving us a lot to think about, which is what we wanted, but I think it would be helpful to have each panel member give us their overall summary of what they think.

DR. BATEMAN: Okay. Alright.

I'm being told by our DFO that we need to go on to break. So we'll take a 10-minute break, and we will return at -- just five minutes. Okay. Let's come back at 4:40, seven minutes.

(Pause.)

DR. BATEMAN: We're going to break for five more minutes before we come back in the session.

(Whereupon, at 4:33 p.m., a recess was taken, and meeting resumed at 4:47 p.m.)

DR. BATEMAN: Okay. Dr. Roca, did you want to --

DR. ROCA: Would you like me to -- what would you like me to do?

DR. BATEMAN: So I was told you're going to explain the question, and the instructions I'm being told is that we should not ask each panel member to respond.

DR. ROCA: Oh, okay. Alright. I understand. Basically, this is not a voting question, first of all. Really, what I was hoping for would be to get a summary assessment of what the people thought about the conversations, and the protocol, et cetera, and specifically, as I mentioned before, whether the design that is under discussion is fit for purpose. It would really help us to hear what each of the panel members think about that, but I also understand, from what I gather, is that you cannot go panel to panel to panel member.

DR. BATEMAN: Yes, those are the instructions I'm being given.

DR. ROCA: Okay.

DR. BATEMAN: So what you're asking for is a global assessment, is the protocol fit to purpose.

DR. ROCA: Exactly. It would help us, because, in truth, we saw quite a bit of really good stuff, and it would be helpful to have somebody say, this is what I think, in the end, of this protocol, but I understand.

DR. BATEMAN: Okay.

Panelists, we won't be going through the roster, but if people are willing to share their thoughts on a global assessment of this approach and the proposed study design, just raise your hand if you'd like to comment on that.

Dr. McAuliffe?

DR. McAULIFFE: I'll step out there. I've been listening all day, and I've done all of the reading from the FDA and the industry, and I've come away with the impression that for me, to use an old-fashioned term, it lacks face validity. I think that the outcomes to me are very predictable.

If you give somebody in a group of chronic non-cancer pain, a select group, 42 weeks of opioid therapy at relatively high doses, or potentially up to 240 milligrams a day, yes, I think that they will have relief of their pain. Now, if you say, when they are taken off of this, will they do better than the placebo group, I'll say, yes, I could predict that they will do better than the placebo group.

What I would prefer to have seen in this is more of a risk-benefit analysis of long-term opioids, not just the risk of hyperalgesia, but as some people were pointing out today, some of the other risks associated with long-term opioids, the CNS risk, the risk of dependency, the risk of tolerance, the GI-associated risks associated with long-term opioids. I think those would be very, very beneficial for clinicians to know. But again, it's just a Gestalt. That's just my opinion. Thank you.

DR. BATEMAN: Okay. Thank you.

Dr. McCann?

DR. McCANN: I have to agree entirely with Dr. McAuliffe. For me, I think the study design was feasible. I think they will be able to enroll patients, but I think it is predictable that if you're doing well with 48 weeks of narcotic treatment, that randomizing them to either get not narcotic or continue, you will find that the narcotic-treated group will do better.

So I think it's just an awful lot of work

for a possibly very predictable answer. It's called enriched enrollment. I almost think it's enhanced enrollment. It's designed to give a positive result before the study's even begun. That's what I feel, so it's possible that you could get a totally different answer, but if I had to guess, I would say it's pretty predictable.

DR. BATEMAN: Thank you.

Dr. Brittain?

DR. BRITTAIN: Yes. I'm kind of sobered by the comments I just heard from my colleagues because I was going to say something different, which I will continue to say, but I do think they certainly raise very important points.

I guess speaking strictly from the vantage point if we accept this question has merit to answer -- and that's the question I thought was posed -- if that's the question that we want to answer, I think the design will probably do a pretty good job of answering that question, whether it's worthwhile answering or not. I do think that's my answer about that narrow question.

I do want to add a couple other summary statements and, again, I am concerned about whether you can really be blinded, so I think one caveat would be some creative solutions to ensure or at least help mitigate those issues. Also, I'm a statistician, so I'm thinking about do we really have power in this study. Of course you want to be sure, if you do this study, that you have the ability to detect a benefit if it's there. Thanks.

DR. BATEMAN: Okay. Thank you.

Dr. Bicket next.

DR. BICKET: This is Mark Bicket at the University of Michigan. I think I have very much appreciated the presentations by the OPC. I think Drs. Argoff, Katz, Angst, and others have responded very well to I think the request from the FDA about putting together the enrolled enrichment randomized withdrawal design after some of the feedback there. I go back to that main question of do opioids remain effective for more than 12 weeks, and the desire to understand both the benefits, if they do outweigh the risks, and how that comes into play.

I do think one of the main concerns about this proposed design is a bit of an underestimation of the potential risks that would be there. The issues with the external validity leading to the generalizability, while the internal validity would be strong, it would have the potential for some difficulty and interpretation, as well as not necessarily providing information that would be as clinically relevant when there is a large opportunity for that, so I would be certainly in favor of thinking about some of these other designs, while I want to appreciate and acknowledge the thought that's gone into the enrolled enrichment randomized withdrawal study. Thank you.

DR. BATEMAN: Okay.

Dr. Sprintz, then we'll go to Dr. Jowza.

DR. SPRINTZ: Hi. It's Michael Sprintz. When answering a question like this, the devil's in the details. I think that's a really important thing, so there are a couple points; one, making the assumption that they actually do a number of suggestions that we had made, it could absolutely

be helpful for a very narrow population, and there are some caveats here.

One, this does not talk about safety; this talks about efficacy, so we need to acknowledge that. Number two, it's a very narrow patient population and we need to be really clear that's what we're talking about, and it shouldn't be extrapolated to chronic pain patients overall. That's one of the problems that got us here in the first place.

The other thing that we haven't really talked about that much -- and I wanted to bring it up earlier -- was the urine drug testing, the urine drug testing and checking the prescription history. Both of those, especially with the drug testing, are really important because of the data. If we don't know what our patients are doing during this whole process, the data's not valid. The data is going to be crap because if we're only testing them once at the screening and then once maybe when we start -- we need to be testing them a lot more during this process, especially during the taper

period. If you're not testing them during the taper period and everyone's doing great, well, we don't really know that, and it's really important.

Drug testing and checking the prescriptions are the only two objective measurements that we currently have to know what our patients are doing when we're not around, and it's really vital that if we're going to draw conclusions from this data, we have to know actually that the data's accurate, because self-reporting in this patient population, when they're facing being taken off of pain medication, we need some other way of verifying. And I think if that is not done, then I don't believe that this study will give accurate data. I believe if they do a good job with drug testing and other forms of making sure the patient is taking what they're taking, not taking what they shouldn't be taking, then you have a much better opportunity for the data to be much more reliable.

DR. BATEMAN: Thank you.

Dr. Jowza?

DR. JOWZA: I'm Maryam Jowza. This is a

very difficult study to design, and it's not the easiest question to answer. So like others have said, I think these are great presentations on both sides.

One of the things that I keep coming back to with the enriched enrollment design is what you're doing in the first 42 weeks is you're determining if opioids are effective for treatment of chronic pain and tolerated; and only then, with that subset of patients for whom opioids are tolerated and possibly effective, you randomize them to either continue with the therapy or to taper, and you're taking a look at what happens when you taper patients for whom opioids were effective and people were able to tolerate it.

I don't know that it answers the question of are opioids -- well, it answers the question, can opioids be safe -- well, not safe, but effective for treatment of pain for the 42 weeks, and that's about it because that's the population that gets to get randomized. And then after that, it answers the question of what happens when you taper that.

And I think that a lot of us are coming into it thinking we wanted something that would be more clinically helpful for us and generalized, but I understand that that's not specifically the question that was asked.

DR. BATEMAN: Thank you.

Dr. Ness?

DR. NESS: I'll try to be brief. I agree with most of those statements that have been made. I agree with Dr. Erica Brittain, which is the very specific question that we're being asked is, are there some people who we can get evidence that they seem to benefit from long-term opioid use? I think this is about the only way that you could do the trial ethically because you can't deny people therapy for a whole year in that sort of a process.

I don't have a major problem with the EERW. I think it will be most valid if you do the gentlest of tapers at the end or use other medicines to limit the side-effect sorts of things with it. I think there will be some useful information. The first 42 weeks will tell you who

definitely fails in opioid, and hopefully our predictors of response will give us some information. We already have some of that information from lots of broad series of these sorts of things, but this would be done in a proper prospective fashion.

So I think there is information to be gained, but the question is just going to be are there some people we got good evidence that they get benefit, and again it's probably predictable based on how it's designed.

DR. BATEMAN: Okay.

Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you. Elizabeth Joniak-Grant. I echo what people have said. I also agree with what Dr. Ness was just saying. I would add I think the function scores are more important than have been currently represented within the current protocol. I don't think that it's designed to necessarily get the answer that opioids work; I think that might be overstating it a bit, but I think what might help balance that is

if the data is collected and analyzed for looking at those who leave before the open-label treatment phase, either because it's not working for them or because they're having side effects. And in the treatment phase, I feel like that group is going to discontinue and they go off into the world. I think if we can have that information as well, that would help balance that sense of bias there.

Then just very briefly, to speak to the comment about urine drug testing, as patients, it gets very tiresome to always hear that the only objective data ever is labs. I think that, yes, it is important. And while I understand as a researcher it's important to check for things and see what people are taking, and trust but verify at times, we also need to tread carefully in that zone because that is a part that chronic pain patients have struggled with for a very long time, a feeling that they're not trusted, that they're seen as addicts, that they're stigmatized, and doing drug testing all the time and things like that really reinforce that.

DR. BATEMAN: Thank you.

Dr. Horrow?

DR. HORROW: Jay Horrow, industry representative. I have a couple of comments. First, I believe that this trial is fit for purpose given that, one, the agency will interpret the results consistent with the population that's randomized; two, appropriate analyses will show consistent results among the pain etiology subgroups; three, the prediction model is suitably constrained to prevent spurious associations; four, the primary endpoint of treatment failure excludes events that arise from non-informative censoring; and finally, that the tapering duration is suitably extended and allows randomly assigned starting times.

However, I think it's important to take the criticism about this being a narrow question with a near specious answer, quote, "designed to succeed," very seriously, and the agency should seriously consider is this a PMR not worth pursuing. In other words, do no study. You've already done ten

others. Is this a randomized clinical trial that is just not worth performing?

Then finally, with respect to a better design, it seems to me the 42-week treatment period has been selected because it's 52 minus 10, and the question is -- what Dr. Ness says about you know what's going on by 6 months as a discriminant -- maybe we could make this a shorter trial duration from 42 down to 26 weeks, and then the 10, or maybe enlarge it to 12 weeks so you'll have a longer slide for the tapering, and make this a shorter study. Will that then answer a question that is worth posing? I don't know the answer to that. Thank you.

DR. BATEMAN: Dr. Shoben?

DR. SHOBEN: Sure. I'll be quick, but a big picture holistic. I think, yes, it's fit for purpose given the articulated concerns about the narrowness of the question, with the caveats that the withdrawal phase does everything it can to minimize the effects of the withdrawal and the loss of blinding, which I think we're going to talk

about in the third question, and with the caveat that I would actually be more what do you assume is true before you do the study. I think we'd certainly assume that you would see an effect of the opioids out at this one-year time point, and they would actually be more concerning to the agency, I would think, if you saw no effect, and to think about what is your prior belief as to what's going to happen when you do the study. Thank you.

DR. BATEMAN: Thank you.

I'll just add my comments. I think there are things to be learned from this trial, but it's addressing a very narrow question. I think addressing the question of whether patients who appear to be tolerating opioids across 42 weeks do better continuing on the opioids versus titrating off is a meaningful question, but it's a pretty narrow one.

I do have concerns about the pace of the taper, and the kind of very, very rapid taper that is proposed will strongly bias towards benefit of treatment. I don't think this really tells us

anything about the most clinically meaningful question for this population, as to whether opioids are a better treatment than non-opioid analgesics or other approaches to treatment. I think that's really where the agency's attention should be focused.

We have examples of trials where patients are randomized to chronic opioid therapy or non-opioid analgesics. I mean, think about the Erin Krebs trial, and I think we're likely to learn a lot more from that type of an approach than what's being proposed here. I guess the other point I would just raise is this does not at all address, obviously, the safety concerns that have been well described in many studies.

Maybe we'll move on to the final question. Question 3, discuss other designs that should be considered in the assessment of long-term effectiveness of opioids.

Dr. Brittain?

DR. BRITTAIN: I keep thinking that maybe we just need to keep randomizing again and again.

There's something called the SMART trial, which I think it's a sequentially multiple assignment randomized trial, where people are randomized initially, and then they're randomized based on how they've done, and then they're randomized again based on how they've done; so if you could imagine a trial that's getting re-randomized every 3 months and covers a year, where nobody who's doing poorly on placebo stays on placebo. I don't know if anything like that would work. It is probably a long shot and would be complicated, but it seems like some sort of re-randomization might be helpful.

DR. BATEMAN: Thank you.

Other thoughts? Dr. Zaafran?

DR. ZAAFRAN: Thanks. Sherif Zaafran from Texas. One of the things that I kept on thinking about as we've been talking about this all day is we've been driving everything toward multimodal and multidisciplinary, and I really don't see in any of these designs anything that kind of combines those elements as we're talking about the long-term use

of opioids.

Dr. Brittain talked a little bit about randomization multiple times, kind of randomizing based on a certain effect, but I think maybe doing that with the effect of multimodal medications, different types of multimodal medications, would be something useful. Obviously, there are different categories, and looking at the impact of one category versus multiple categories in conjunction with an opioid on long-term use and how effective it is, I think is useful, because one of the questions that I keep asking myself is, it's not about whether long-term use of opioids is effective or not, but it's can I get the same effect with a significantly lower amount of opioid usage and have a stronger impact, especially as we measure what pain looks like from a quality standpoint as opposed to from a subjective standpoint.

So that's the only thing I would consider, is putting a lot of that into how we design the study and appreciating it that way.

DR. BATEMAN: Thank you.

Other questions or other thoughts?

Dr. McAuliffe.

DR. McAULIFFE: I think it would also be very important to include some measures of functionality, as many people have mentioned, and somebody also mentioned a qualitative arm to this, where you could get really some very rich data about the risks and the benefits of opioids.

DR. BATEMAN: Thank you.

Other comments?

(No response.)

DR. BATEMAN: If people want to comment on thoughts about a more traditional RCT, where patients would be randomized to chronic opioid therapy versus non-opioid analgesics; is that potentially a better approach to get at this question of long-term effectiveness?

Dr. Zaafran?

DR. ZAAFRAN: Again, yes but no. The way you asked the question was almost like an either/or, long-term opioids versus non-opioids. Again, I go back to combination versus only, and

what that combination looks like, and randomizing based on that way.

DR. BATEMAN: So non-opioid analgesics plus opioids versus not.

DR. ZAAFRAN: Well, not just non-opioid analgesics, but one category versus several categories, versus another category, versus none at all. I don't know the impact of acetaminophen plus an opioid, acetaminophen plus a non-steroidal plus an opioid, or only a non-steroidal plus an opioid. There are so many different variables there, that I think we need what is the right combination that has the most amount of impact.

DR. BATEMAN: Okay.

Dr. Bicket?

DR. BICKET: Yes. Mark Bicket at the University of Michigan. I do appreciate the comments about thinking of other trial designs. I do think the inclusion of a placebo, to some degree, is valuable. It doesn't necessarily have to be the end-all, though, if there are appropriate comparators for which we have great evidence. We

do know that patients who will receive treatments and have a greater likelihood of being randomized to treatments are more likely to want to participate in the trials. There can be some burden I think with trying to mask some of those treatments or understanding the degree to which blinding does need to be achieved, but there could be some creative ways in terms of incorporating these prior suggestions and thinking about whether it's a bit of a derivation of these adaptive interventions that use the smart designs.

It's obviously a sophisticated approach, but could integrate both non-opioid treatments as well as non-pharmacologic treatments, because I do think both of those, for ones that do have efficacy already established, would likely help individuals want to participate, knowing that they have a likelihood of having these different therapies through which an appropriate statistical design could somehow try to tease apart the value out of this long-acting opioid that goes in.

Apart from that, just one other comment

about more traditional parallel design studies, where they include placebos. They certainly, as mentioned before, are quite challenging. We did see examples of this in the veteran population, where there's an open-label with an active comparator. Still, I would imagine, if you'd speak with Erin Krebs, would probably explain to you about some of the challenges with patient recruitment and retention and the strategies they employed.

That certainly goes up a notch if blinding happens, so I want to be cognizant about that but recognize that success could be there with some different approaches that certainly start to engage patients in that process of how to best recruit and retain them. Thank you

DR. BATEMAN: Okay.

Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you. Elizabeth Joniak-Grant. I think the idea of doing comparisons, looking at multimodal use is wise, especially because that more accurately reflects

the reality of patients that are getting care for chronic non-cancer pain. And then Dr. Bicket kind of beat me to it, where I don't think that having a placebo in the sense that you don't have anything would work very well. I don't think it's very ethical to ask patients who are suffering to wait, but if they could maybe balance that with doing certain types of non-pharmacological, I think that would would work for people and recruitment. A lot of patients are looking for those options as well.

DR. BATEMAN: Okay. Thank you.

Any other final comments on question 3?

(No response.)

DR. BATEMAN: I think just maybe to summarize the points, some people did express some enthusiasm for approaches that compared opioids to either pharmacologic or non-pharmacologic opioid alternatives, recognizing the limitations associated with some of those designs and the challenges of those designs.

I think there's general consensus that randomizing patients to placebo versus an opioid is

going to be incredibly challenging, and that certainly is the experience that was had in the earlier version of the trial that the FDA undertook, but I think there's also perhaps the desire to look at some creative and innovative approaches to randomization that could be run across the period of a year where there was sequential randomization or other innovative approaches to help us address some of these questions in a way that would be possible to recruit patients into and retain them in the trial as well.

Anything people want to add to those thoughts

(No response.)

DR. BATEMAN: Okay. So I think we've come to the end here. I thank the panel for a very engaging discussion and I think a lot of good feedback to the FDA on the questions that they raised.

Before we adjourn, any last comments from the FDA?

DR. ROCA: This is Dr. Roca. I just wanted to say thank you very much for your comments and the discussion. We certainly appreciate it, and we'll take them back for internal discussions as well, and thank you. Have a nice day.

Adjournment

DR. BATEMAN: Alright. We'll now adjourn the meeting. Thank you all very much.

(Whereupon, at 5:17 p.m., the meeting was adjourned.)