FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEETING (PDAC)

Tuesday, March 27, 2018

8:00 a.m. to 3:11 p.m.

Tommy Douglas Conference Center

10000 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. NARENDRAN: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Michael Felberbaum. If you are present, please stand. He's over there at the corner.

My name is Raj Narendran. I'm the chairperson for today's meeting. I will now call the Psychopharmacologic Drug Advisory Committee meeting to order. We'll start by going around the table and introduce ourselves. We'll start with the FDA to my left and go around the table.

DR. THANH HAI: Good morning. I'm Mary Thanh Hai. I'm the deputy director in the Office of Drug Evaluation II.

DR. WINCHELL: I'm Celia Winchell. I'm the medical team leader for addiction products in the

Division of Anesthesia, Analgesia, and Addiction Products.

DR. HORN: Good morning. My name is Pamela Horn, and I'm the clinical reviewer in the same division.

DR. REN: Good morning. I'm Yi Ren. I'm the statistical reviewer at the Office of Biostatistics at FDA.

MR. PETULLO: Good morning. David Petullo, statistical team leader, Office of Biostatistics.

DR. FIEDOROWICZ: Jess Fiedorowicz, PDAC member, physician/scientist at the University of Iowa.

DR. DUNN: Good morning. Walter Dunn. I'm assistant professor at UCLA.

DR. JAIN: Good morning. Felipe Jain, a psychiatrist at Mass General Hospital now.

MS. BHATT: Good morning. I'm Kalyani Bhatt. I'm the designated federal officer with the Division of Advisory Committee and Consultant Management.

DR. NARENDRAN: I'm Raj Narendran,

psychiatrist at the University of Pittsburgh.

MS. BHATT: Dr. Jeffrey, can you please introduce yourself via telecon?

DR. JEFFREY: Yes. Hi. This is Jessica Jeffrey. I'm an assistant clinical professor at UCLA.

MS. BHATT: Thank you.

DR. TURNER: Good morning. I'm Erick Turner, a psychiatrist at Oregon Health and Science University and the VA Portland Health Care System.

DR. PICKAR: Dave Pickar, adjunct professor of psychiatry at Hopkins and Uniformed Services.

MS. WITCZAK: Good morning. Kim Witczak, consumer representative.

MS. NUMANN: Sabrina Numann, patient representative.

DR. PROSCHAN: I'm Michael Proschan, mathematical statistician at the National Institute of Allergy and Infectious Diseases.

DR. BRADY: I'm Kathleen Brady. I'm a psychiatrist from the Medical University of South Carolina.

DR. CARROLL: Hi. I'm Kathleen Carroll. I'm a psychologist at Yale University School of Medicine.

DR. CONLEY: Good morning. I'm Rob Conley. I'm a psychiatrist and the head of late-phase neuroscience development at Eli Lilly and a professor of psychiatry and pharmacy science at the University of Maryland. I'm here as the industry representative.

DR. NARENDRAN: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for the discussion of these issues, and those 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 the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with all media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I'll pass it to Kalyani Bhatt, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

MS. BHATT: Good morning. The Food and Drug Administration is convening today's meeting of the Psychopharmacologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal

conflict of interest laws and regulations.

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

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

Related to the discussion of today's

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

Today's agenda involves the discussion of new drug application, NDA 209229, lofexidine hydrochloride, submitted by US WorldMeds LLC, for mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment.

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

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

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

We'd like to remind members and temporary voting members that if the discussion involves any other product or firm that's not already on the agenda for which an FDA participant has a personal imputed financial interest, the participants need to exclude themselves for such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have

with the firm at issue.

DR. NARENDRAN: Thank you.

Dr. Hertz, do you want to introduce yourself?

DR. HERTZ: Yes. Thank you. Good morning. I'm Sharon Hertz, division director for the Division of Anesthesia, Analgesia, and Addiction Products.

DR. NARENDRAN: We will now proceed with the FDA's introductory remarks presented by Dr. Celia Winchell.

FDA Opening Remarks - Celia Winchell

DR. WINCHELL: Good morning, Dr. Narendran, members of the Psychopharmacologic Drugs Advisory Committee, and invited guests. Thank you for your participation in this important meeting. Today we'll ask your assistance in our evaluation of US WorldMeds' application to market lofexidine oral tablets to treat the symptoms of withdrawal from opioids. Specifically, lofexidine has been studied to really withdraw symptoms after abrupt discontinuation of opioids, and thereby to

facilitate completion of what is customarily been called detoxification, leading the patient to an opioid-free state. And I'll just mention that the term "detoxification" is not currently used much, but we'll probably use it for convenience in these presentations and discussions today.

My next slide -- if you were to be able to see it -- would say outline, and it would tell you what I'm going to talk about, so I'll just keep talking. Opioid withdrawal symptoms may occur in the context of discontinuation or dose reduction of opioids in anyone who's been exposed for a sufficient duration to develop physical dependence. Withdrawal symptoms are not specific to patients with opioid-use disorder or addiction, however, withdrawal symptoms may have a particular salience and significance for patients with addiction.

Many patients with addiction find the physical and psychological distress of withdrawal, or even just the prospect of it, a major obstacle to entering treatment. One option for treatment of opioid-use disorder is maintenance with agonist or

partial agonist medication. That allows many patients to gain control over their drug use behavior and achieve rehabilitation without undergoing discontinuation of opioids.

This treatment approach is well established and well supported, but for many patients, at one time or another, there might be reasons that it becomes necessary or preferred to withdraw completely from opioids. This morning I'll discuss the rationale for treating opioid withdrawal symptoms with non-opioid medications, I'll provide some historical background, and then I'll describe the focus for today's meeting.

There is only one medication with a labeled indication for detox, as you probably know, but several have been studied. For patients with opioid-use disorder, the goal of entering detox is to reach a state of not being physically dependent on opioids. There have been a number of studies of medications to be used during opioid detoxification that use various approaches to measuring the effects.

There are a whole bunch of different instruments to document the intensity of observer-rated signs. There are different instruments for patient-reported inventories of symptoms. There are analyses of time to drop out or completion rates. But clinically, when managing the symptoms of withdrawal, our objective is to minimize the patient's unpleasant subjective experiences so as to encourage the patient to reach the goal of finishing the detox. And a drug that exerts its effects on signs like pupil diameter or hypertension might not really have an effect on a patient's experience.

If the patient doesn't complete the discontinuation process to the end of the withdrawal symptoms and relapses to opioid use in the middle, then the treatment goal hasn't been reached. So in essence, the clinical importance of the ability to mitigate withdrawal symptoms is actually confirmed by the product's ability to improve the rate of patient's success in completing the discontinuation.

(Technical difficulty with slide presentation.)

I should be on my slide 4. That's all right. Slides are not important. I just made these slides so you wouldn't get bored while I was talking, so I'm just going to keep talking.

Arnold Washton and Richard Resnick, writing in the Journal of Pharmacotherapy in 1981, provided this helpful view. "The primary objective of opioid detoxification is to provide symptomatic relief from the withdrawal syndrome while physical dependence on opiates is being eliminated."

Although the withdrawal syndrome is only one of many factors that perpetuate addiction, it is nonetheless an important one since many addicted individuals find the physical and psychological distress of withdrawal a major obstacle to achieving an opioid-free state. While it's generally unrealistic to aim for permanent or even long-term abstinence as an outcome of detoxification treatment alone, when viewed in the context of a multimodality treatment approach,

detoxification plays a number of important roles.

For example, it is the first step toward opioid-free functioning and a gateway to other modalities such as drug-free and opioid antagonist treatment. Because for some addicts, detoxification treatment represents the first contact with the treatment system, it may be critical in fostering continued involvement in the rehabilitative process.

The only drug that has a labeled indication for use in detoxification treatment is methadone, and the authors noted that any opioid medication can prevent or reverse withdrawal symptoms. But all of these drugs have their own potential for abuse and lead to essentially the same abstinence syndrome when discontinued, therefore, it's desirable to have a non-opioid agent that could relieve withdrawal symptoms without itself producing physical dependence or euphoria.

That leads us to alpha agonists. Although opioid medications have been used since antiquity, the studies that identified the role of the

adrenergic system in opioid withdrawal were first published in the 1970s. Clonidine, an alpha-2 adrenergic agonist, was at that time a new antihypertensive, and it was reported to have effects on opioid withdrawal in animals and humans. The 1970s also saw significant research on opioid antagonists for the treatment of addiction, primarily oral naltrexone. And because patients must be fully withdrawn from opioids before beginning antagonist therapy, the development and approval of oral naltrexone also fostered interest in non-opioid drugs for management of withdrawal symptoms.

Clonidine was approved as a hypertensive in 1974, and a number of studies were conducted demonstrating its utility in treating the symptoms of opioid withdrawal. However, the cardiovascular effects such as hypotension, orthostasis, syncope, bradycardia were concerns that initially limited the use of clonidine to inpatient settings where patient could be suitably monitored.

Interest in lofexidine, which is another

alpha agonist drug with putative antihypertensive properties, was driven by the impression that lofexidine was not a very good antihypotensive and therefore might be better tolerated than clonidine. There were a number of both clonidine and lofexidine, including studies comparing the two to each other, and the prevailing conclusion was that lofexidine was as effective as clonidine but had fewer side effects such as sedation and hypotension. But clonidine was marketed, and lofexidine wasn't, so clonidine really became more or less the standard of care in treating withdrawal.

The development of lofexidine continued in a slow but steady manner, very, very slow. It was eventually approved in the UK for treating opioid withdrawal at a typical dose of 1.6 milligrams per day -- you should remember that -- and in 2016, a Cochrane review of alpha agonists -- really just clonidine and lofexidine, and maybe a little guanfacine in there -- was done, and they noted that the studies that used lofexidine used maximum

doses of 1.6 milligrams per day to 2.6 milligrams per day. Their summary was that alpha-2 adrenergic agonists are typically administered orally as 2 to 4 doses per day with the total dose adjusted daily according to withdrawal symptoms and side effects, particular blood pressure.

Clonidine is generally commenced at 0.1 milligrams per dose to 0.2 milligrams per dose, increasing to a maximum of around 1 milligram per day, and lofexidine at 0.4 milligrams per dose to 0.6 milligrams per dose, increasing to a maximum of around 2 milligrams per day. Maximal doses are generally administered for only a few days around the time of maximal withdrawal, usually 2 to 4 days after cessation of opioids. Doses are then tapered and ceased 7 to 10 days after the cessation of opioids. We have lofexidine approved in the UK. Dose is typically 1.6 milligrams per day. Maximum dose mentioned in the Cochrane review, 2 milligrams per day.

In 1995, when the lofexidine development program we'll be discussing today began in the

U.S., the initial protocol was a pilot study, and the dose was 1.6 milligrams per day initially, but the first cohort had a disappointing rate of completing treatment. The study showed effects on certain measures of withdrawal, but the low rate of completion raised concern that the magnitude of effect on withdrawal was insufficient to yield clinical benefit.

The protocol was amended to allow cohorts at higher doses, first at 2.4 milligrams per day, and then at 3.2 milligrams per day, and finally at 4 milligrams per day. Then the sponsor decided the optimal dose to pursue was 3.2 milligrams per day. Now, that's twice the customary dose. Even at 2.4 milligrams per day, there were discontinuations due to adverse effects, and unquestionably, higher doses of lofexidine caused bradycardia, hypotension, and syncope. So the putative advantage over clonidine as effective with less hypotension was unlikely to be retained if lofexidine doses were significantly elevated beyond this 1.6-milligram per day that had previously been

studied.

In the interest of identifying an optimally effective dose, the sponsor moved forward first with a study of the effects of high-dose lofexidine on withdrawal signs, not symptoms, and then with a second study of the same dose using an instrument to measure effects on subjective symptoms, and neither of these studies included a dose below 3.2 milligrams per day. It was an issue that the division did point out at various advice meetings.

After completing two studies, the sponsor proposed to submit the new drug application, and the division was forced to point out that there were a few shortcomings. There was one study of signs that didn't actually show an effect on symptoms. There was study of symptoms and that these two together didn't add up to a claim for symptoms. The duration of exposure in the studies didn't match up with the way the product was typically used, and the data did suggest presence of rebound hypertension that had not been well evaluated.

To address these concerns, the sponsor undertook collection of additional information to support the application. They did a whole additional controlled study, including a lower-dose arm, and this is the 2.4-milligram per day dose, still higher than the typical dose used in the UK. This study also provided additional information on the effects of lofexidine on subjective symptoms of withdrawal, and they compiled a submission to support the appropriateness of the patient-reported outcome instrument used in the studies, so that brings us to today.

Today you'll hear information about the safety and efficacy results of the two pivotal studies, and we'll ask you to consider whether they provide support for the proposed indications. In this application, US WorldMeds has proposed two claims about lofexidine's efficacy to be included in the indication section of labeling and their mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment, which we acknowledge is

a mouthful.

The proposed regimen is 4 0.2-milligram tablets 4 times a day for 7 days, so that's 3.2 milligrams per day regimen. First we will ask you to discuss the relationship between the two concepts, the mitigation of symptoms of opioid withdrawal and the facilitation of completion of detox. We'll ask you whether the data support both claims and to discuss whether these really are separate claims that can be considered to have meaningful benefit in and of themselves.

Would it be possible for a sponsor to make a claim of symptomatic relief if they didn't also provide evidence that the effect translates to improvement and completion of detoxification? If a patient is comfortable enough to tolerate withdrawal and to remain opioid free until withdrawal is complete, the clinical meaningfulness is clear. But if the patient has some relief of symptoms but is still too uncomfortable to complete withdrawal, can we conclude the amount of relief was not clinically relevant?

The putative advantages of lofexidine over clonidine is that it has fewer adverse effects such as hypotension and sedation, however, those advantages were established at doses about half the dose studied in the sponsor's trials. The data indicate that lofexidine is associated with a number of dose-limiting adverse effects such as hypotension, bradycardia, and syncope. We'll ask for your thoughts on what dose regimen should be recommended.

Some other gaps exist in the data. The clinical data submitted in support of this application provide very limited exposure beyond 5 days of dosing, so a new molecular entity. Patients may undergo multiple cycles of detoxification and could be exposed to lofexidine for significantly more than 5 days. That would particularly be the case if lofexidine were used in a context of a gradual opioid taper.

The efficacy of lofexidine of course has only been demonstrated in patients discontinuing opioids abruptly, and many patients discontinuing

opioids do so gradually. The symptoms of withdrawal can often be mitigated by slowing the taper, but we can reasonably expect that once lofexidine is available, patients and clinicians might be interested in using it in the context of gradual opioid taper both in patients with opioid-use disorder and in patients without opioid-use disorder who are completing a course of opioid analgesic treatment.

We don't have any evidence showing benefit of lofexidine when it's used in this extremely common scenario, so this is a concern, particularly given the observation that lofexidine might have effects on cardiac conduction, perhaps not clinically significant when used on its own but may be more so in conjunction with other drugs that prolong the QT interval, which notably includes methadone and to a lesser extent buprenorphine.

We will ask you how this information gap would be best addressed. Your deliberations and recommendations will play an important role in our decision-making process, and I would like to thank

you for taking time from your other extensive responsibilities to participate in this meeting.

DR. NARENDRAN: Thank you, Dr. Winchell.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have 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 US WorldMeds' presentation.

Applicant Presentation - Kristen Gullo

MS. GULLO: Good morning. My name is Kristen Gullo. I'm vice president of development and regulatory affairs for US WorldMeds. Before I start, I'd like to confirm that all of our external speakers and responders have been compensated for their time and expertise, but otherwise have no financial interest in the company or product. I'd like to thank the FDA for the opportunity to present the lofexidine program. I'd also like to thank the committee members for their time reviewing the materials for this meeting.

US WorldMeds is a specialty pharmaceutical company located in Louisville, Kentucky. We recognize that a company's location is not generally of much importance, but in the case of the opioid crisis, Kentucky has been one of the earliest and hardest hit by prescription opioid misuse and abuse, and we continue to face

prescription pain medication and heroin overdose death rates among the highest in the nation.

My colleagues and I at US WorldMeds consider it a privilege to discuss the opportunities that successful management of opioid withdrawal represents in the fight against the opioid epidemic. We realize that implementing solutions for the opioid crisis will be complex and that this development, while important, addresses only one part of a complicated picture. With that in mind, we welcome your input and guidance during this meeting to understand how we can enhance the utility of lofexidine for the greatest benefit to patients if approved.

Dr. Baxter will begin today's presentation with a discussion of the current landscape of opioid withdrawal management. I will return to provide an introduction to the lofexidine development program. Dr. Fishman will review the rationale and methodology employed in the lofexidine clinical trial program. Dr. Gorodetzky will review clear and consistent benefits of

lofexidine that have been established across a robust clinical program.

These studies show that compared to placebo, lofexidine treatment is associated with less severe symptoms as reported through multiple patient- and rater-completed assessments, which correlated with improved completion outcomes. Dr. Pirner will review the findings from out safety analyses, which showed that lofexidine is well tolerated with few side effects that are manageable and consistent with the well characterized alpha-2 agonist drug class.

Dr. Kosten will conclude for us with his clinical perspective, sharing insights on why lofexidine represents an important treatment addition for opioid withdrawal management and how it can be used to facilitate opioid discontinuation in physically dependent patients. He will also discuss why withdrawal management is vital to creating opportunities for continuation of care in opioid-dependent patients and the consequences for patients who are unable to successfully withdraw

from opioids.

Dr. Baxter?

Applicant Presentation - Louis Baxter

DR. BAXTER: Good morning. I'm Dr. Lou Baxter. I currently s**erve as the executive medical director of the professional** assistance program of New Jersey, treating impaired healthcare professionals. In the past, I've served as an officer of organizations dedicated to substance use treatment. I've advised on national drug control policy during the Clinton, Bush, and Obama administrations. I'm also affiliated with Rutgers and Howard Universities, but most importantly, though, I am a doctor. I'm a clinician, and I have been treating patients with substance use disorder for more than 30 years. I actually treat patients who have opiate dependence.

We are all aware of the complexity of the state of opiate use in the United States. I've seen opiate-dependent patients from all walks of life struggle with the challenge of withdrawal. I've watched many of them fail to complete the

withdrawal process. That's why I'm so excited to be here and to participate in this discussion today.

Physical dependence on opiates develop with prolong exposure, which causes actual changes in brain chemistry. In some patients, physical dependence leads to opiate-use disorder as defined by detrimental, psychological, and behavioral features. When patients with a strong physical dependence on opioids stop or sharply reduce opiate use, whether with or without opioid-use disorder, they will experience the acute, distressing effects of opiate withdrawal syndrome.

This syndrome is a constellation of physical and emotional symptoms resulting from disruptions in the brain chemistry. It is defined by a set of symptoms, many or most of which are associated with heightened adrenergic activity that include anxiety, pain, nausea, muscle aches, cramping, sleep disturbances, vomiting, runny nose, sweating, tachycardia, and diarrhea.

The patient's experience of the syndrome is

highly individualized. Some people have leg twitching and profuse sweating; some don't. Some experience abdominal cramping and joint pains and myalgias, and some don't. Patients experience some symptoms with high intensity and others with low intensity. The intensity also varies from patient to patient. Some patients say, "I feel like I'm dying," and I can see it. I can actually see the fear in their faces.

Acute opiate withdrawal symptoms are severe generally peaking in severity within 2 to 4 days after the last use of the opioid. Although they will resolve over a course of 1 to 2 weeks untreated, 1 to 2 weeks of distress, and especially those 2 to 4 days of the highest intensity of discomfort, is often a deal-breaker for patients, and that causes them not to continue through the withdrawal process. Many of the patients also have comorbid conditions and can become destabilized during withdrawal. This makes the withdrawal experience even more difficult to manage. The most controllable variable affecting success and

retention is to make the experience less physically distressing.

The impact of the opioid withdrawal syndrome on patients is illustrated in the prescription opioid addiction treatment study conducted in 2014. The study included 653 patients with physical dependence on opioids, both with and without chronic pain. The study used a survey to assess reasons for initial use and current use of opioids among the participants. Both cohorts of patients rated avoiding withdrawal as the single highest scored reasons for concurrent use of opiates.

Avoiding or abandoning withdrawal has significant repercussions. These patients run the risk of developing or worsening opioid-use disorder leading to potential social and criminal consequences, the risk of overdose, and death. Our job as physicians is to help manage withdrawals so that they can transition into subsequent stages of care.

Most patients with opioid dependence will face withdrawal at some point in their journey to a

planned transition to subsequent treatment. For these patients, managing withdrawal successfully is a most essential step towards that transition. Simply put, successful withdrawal management is a critical component for the opioid-use disorder patients, desiring comprehensive, long-term recovery.

A subset of opioid-use disorder patients is presently maintained on opioid agonist medications to facilitate their recovery. However, for those who might need to or want to discontinue their use for personal or professional reasons, overcoming the withdrawal barrier is equally significant. And finally, many patients treated for pain become dependent on opioids. They too will experience opioid withdrawal that must be managed.

Let's discuss the options we currently have for managing withdrawal. The only FDA-approved medication for acute opioid detoxification is methadone, although buprenorphine is frequently used off label in a similar manner. Although both of these opioid-based medications are successful at

addressing withdrawal symptoms and getting patients through the withdrawal barrier, they also both have challenges, notably risk of diversion and abuse.

Methadone and buprenorphine require special licensing, making them unavailable to many physicians who are not so licensed. Even when they are available, withdrawal treatment with agonist medications can make the withdrawal process lengthier. These options are not appropriate or preferred for all patients and treatment goals.

Although clonidine is not approved for treatment of opioid withdrawal, it has been used for more than 30 years. It is regarded as a largely effective therapy, although it is poorly tolerated in some patients. Moreover, its use is limited because of lack of clear dosing guidelines. Physicians newer to managing withdrawal are less comfortable using it.

Tapering of the primary opioid is also used to manage withdrawal. It is specifically recommended for patients discontinuing opioids for analgesic use who have developed dependence and for

patients for whom discontinuation of agonist medication assisted therapy is necessary or desired. However, the taper process is not well defined in either situation, thus many provider-specific protocols have been developed. These withdrawal taper protocols are variable in length and levels of success in managing symptoms. In addition, some of these protocols simply do not work.

The limitations of the withdrawal management approaches I just discussed prevent us from dealing effectively with the opioid crisis. So what do we need? We need non-opioid therapies that have been properly studied in patients seeking treatment for opioid dependence, and we need the ability to put these medications in the hands of healthcare professionals. We need evidence-based treatment guidelines to provide both specialists and the broader healthcare community with the knowledge they need to manage the withdrawal process. Particularly, when opioid taper is unsuccessful or is not desired, we simply have insufficient

pharmaceutical options to manage withdrawal. Now that we know what is available, here is the process involved in identifying patients and their appropriate treatment.

In addition to a thorough medical exam, patient selection for medically managed withdrawal begins with a patient interview to assess their personal situations. One consideration that predicts patient success is self-motivation. Withdrawal is almost always more successful when the patient's motive comes from within rather than from an external source.

Assessment of the patient's support system is also important to make determinations about withdrawal options and placement in an appropriate setting. Because of the intensity of physical symptoms and because of the need for encouragement, patients often need help going through the process. For some, institutional support is essential. For those in office-based withdrawal, the engagement of a spouse, a friend, parent, or even a sponsor is also essential.

In addition, doctors and patients have to establish appropriate expectations about the withdrawal experience, and patients have to be able to follow caregivers' instructions about how to conduct themselves in their chosen withdrawal setting. The best candidates for managed withdrawal are those with planned appropriate post-withdrawal care, which is particularly critical if they have opiate-use disorder.

Finally, patients with opiate-use disorder need a placement assessment with the criteria established by the American Society of Addiction Medicine's criteria. It includes assessment of psychiatric comorbidity, the existence of other chronic medical problems, the severity of the use disorder, and a history of prior treatment successes or failures. These criteria are used to place patients in a proper level of care both for withdrawal and for post-withdrawal intervention.

There are three important facts related to managing opiate withdrawal. First, patients physically dependent on opioids attempting to stop

will undergo withdrawal. Secondly, the intensity of the distress caused by opiate withdrawal is significant, and it creates a barrier to completing opioid discontinuation and subsequent treatment, and the risks to the patient who should stop opioid use and can't are great.

We have been caught unprepared for the crisis we face today. To face it, we need an all-hands-on-deck approach. We need help from pain managers, psychiatrists, addictionologists, family practitioners, from all those who have the power to help patients through withdrawal. In the rest of today's presentations, you'll hear about the lofexidine program and its result, and you will have the opportunity to assess its potential to help overcome the withdrawal barrier.

Vice president?

Applicant Presentation - Kristen Gullo

MS. GULLO: As we heard from Dr. Baxter, the opioid epidemic is complex, and it will require a community effort to ease the devastation it causes. At US WorldMeds, we have a heightened sense of

responsibility to contribute to solutions for the opioid crisis. This is not just a national problem; this is in our own backyard. I'll take you briefly through the lofexidine development rationale and history and further detail the neurobiology of withdrawal. I'll then discuss lofexidine's mechanism of action that drives the efficacy results and safety profile we will review later today.

Lofexidine is the first non-opioid, non-addictive product developed for use in opioid withdrawal management. It is a selective alpha-2 adrenergic receptor agonist with no other clinically relevant receptor activity. Specifically, there is no meaningful activity on receptor groups associated with abuse potential.

Lofexidine is not a long-term addiction recovery aid. It is not a replacement for opioid agonist- of antagonist-based medication-assisted treatments in patients who have developed use disorders. However, it is a medication complementary to existing indicated treatments to

address an unmet need for the treatment of opioid withdrawal syndrome in dependent patients. Specifically, the proposed indications for lofexidine are for the mitigation of symptoms associated with opioid withdrawal and for the facilitation of completion of opioid discontinuation treatment.

Lofexidine has been developed as a 0.2-milligram tablet. The proposed dose is 3.2 milligrams per day delivered in 4 increments of 0.8 milligrams for 7 days. The low-dosage tablet and the QID regimen allow flexibility in dosing when necessary. An additional 7 days of treatment is proposed when determined appropriate by the physician with dosing to be guided by symptoms.

As Dr. Baxter discussed, alpha-2 agonists such as clonidine have been used off label in the treatment of withdrawal for decades. This is despite limited data supporting dosing and benefit-risk characterization. Lofexidine, which is also an alpha-2 receptor agonist, showed promising results for this indication and was

acquired by a company in the United Kingdom. This was in response to a significant public health need related to opioid withdrawal occurring in the correction system.

The company submitted a limited regulatory package, which was considered for approval in the UK. The UK approved product has been used consistently for the past 25 years across a variety of settings, including community-based treatment. Guidelines from the National Institute for Health and Care Excellence in the UK, or NICE, recommend its use in opioid withdrawal. This provides further support for the positive benefit-risk profile of lofexidine in withdrawing patients.

Based on the UK experience, the National Institute on Drug Abuse initiated development work in the United States. Subsequently, NIDA partnered with US WorldMeds to undertake completion of registration requirements. We licensed the product in 2003 and have worked continuously since that time to bring it to market in the U.S. This was in recognition of the unmet need for opioid withdrawal

treatment, a need which, as you know, has grown over the course of its development.

Since US WorldMeds became sponsor of lofexidine, we have completed comprehensive development activities required for the introduction of a new chemical entity to the United States. This includes complete drug substance and drug product campaigns, modern nonclinical studies to assess safety margins, and a substantial clinical program. The clinical studies were navigated with input from FDA and collaborative scientific and funding support from the National Institute on Drug Abuse.

The clinical portion of our application is comprised of a total of 24 studies, including 16 clinical pharmacology studies, 4 supporting safety studies, and a phase 3 program which also includes 4 studies, two of which are pivotal studies to support efficacy claims. The pivotal studies we will present to you later today includes study 2 and study 3-1.

Consistent with our proposed indications,

our development program focused on treating physically-dependent patients experiencing withdrawal as they stopped opioids. Our study population is representative of opioid-dependent patients who would seek treatment for withdrawal.

The total development program included studies with inpatient and office-based treatment components and generated a safety database comprised of over 1200 total patients. Over 1100 of these were opioid-dependent patients undergoing withdrawal in a variety of treatment scenarios.

The program has been focused on the need for a non-opioid, non-addictive, and well studied treatment for use in opioid-withdrawing patients. The experiences of patients in withdrawal that you heard from Dr. Baxter paint a picture far beyond discomfort. It's agony. It's an agony that lasts for a week and sometimes longer, and it is a significant barrier for many opioid-dependent patients to reach the next step in their treatment.

There are complex brain changes that are associated with opioid dependence and withdrawal.

These changes are largely centered around norepinephrine levels, which surge when opioids are abruptly stopped in a physically dependent patient. Norepinephrine production is altered in the brain following repeat exposure to opioids. In the withdrawing patient, norepinephrine levels are temporarily increased due to the lack of offsetting opioids.

Alpha-2 adrenergic receptors, when activated, inhibit norepinephrine release from the presynaptic neurons. Lofexidine as a selective alpha-2 adrenergic receptor agonist thus stimulate these receptors, which in turn reduces the norepinephrine level and alleviates the norepinephrine driven symptoms in the withdrawing patient. Our understanding of the mechanism of action aided in guiding the evaluation of risks and benefits anticipated with lofexidine treatment and informed the design of the clinical program, which will now be discussed by Dr. Marc Fishman.

Applicant Presentation - Marc Fishman

DR. FISHMAN: Good morning. Thank you for

the opportunity to present today. I'm an addiction psychiatrist, clinician, and researcher with 25 years experience in the treatment of opioid dependence in both patients with opioid-use disorder and chronic pain. But most relevant to today's presentation, I was an investigator for two of the lofexidine trials that we will present today. In fact, the program where I was the site PI, Avery Road Treatment Center, is just a few miles away from here. Because of that role, I have firsthand understanding of the design and implementation of these studies. My task today is to introduce the goals and design of the trials supporting the efficacy and safety of lofexidine.

The program was designed to focus on a withdrawal scenario of full abrupt cessation of opioid use. This scenario is most commonly encountered in patients with opioid-use disorder who are seeking transition to non-opioid treatment. Following the completion of two pivotal studies of abrupt cessation, an open-label safety study was conducted to accumulate additional experience and

safety data in other clinical scenarios of potential utility for the field such as withdrawal management during opioid dose reduction and as an adjunct treatment during agonist-assisted withdrawal.

I will focus my discussion on these three studies: pivotal efficacy studies 2 and 3-1 and the open-label safety study 3-2, which more closely resembled withdrawal management in usual clinical practice.

Pivotal study 2 evaluated lofexidine 3.2 milligrams per day compared with placebo. In this study, the active treatment period was 5 days with lofexidine versus placebo followed by both groups receiving placebo for days 6 and 7. The total end was 264.

Pivotal study 3-1 evaluated two different doses of lofexidine, both 2.4 milligrams per day and 3.2 milligrams per day compared with placebo using a randomization scheme of 3 to 3 to 2 with a planned treatment for a duration of 7 days. An additional optional 7 days of open-label lofexidine

treatment was available for patients at investigator and patient discretion. A total of 603 patients were randomized.

The two studies have two important differences. Number one, addition of the second dose in the second study, 3-1, and number two, extension of the controlled treatment period from 5 days to 7 days to evaluate benefits of the full course of the withdrawal intervention.

The open-label safety study 3-2 enrolled 286 participants who initially received lofexidine 3.2 milligrams per day. After the first dose, investigators could choose to reduce the dose to 2.4 milligrams per day. Treatment began with a mandatory 3-day stay in a bed-based setting. Patients could be then discharged to ambulatory status with lofexidine treatment continuing for the remainder of the prescribed 7-day course, again, with an option to continue for an additional follow-on period of 7 days of continuation of lofexidine in open-label treatment.

There was considerable heterogeneity in the

sites, although all were bed based because of the considerable data collection associated with the research and the result in patient burden that was required for the protocols. The sites ranged from private clinical research centers, to academic research unit, to community hospital units, and community treatment substance-use disorder programs like the one where I was a site PI.

If it hadn't been for the protocol requirements, patients enrolled in this bed-based study would likely have been treated in an even greater variety of settings, and determinations for those treatment placements and practice would generally be done in accordance with the American Society of Addiction Medicine criteria, or ASAM criteria, that Dr. Baxter referenced, further influenced by local practice, local referral flows, and local resource availability.

For the two pivotal studies, the protocol required full and abrupt cessation of opioids to try to standardize as much as possible the withdrawal syndrome and also to isolate the effect

of lofexidine. For these studies, heavy use of short-acting opioids, that is 21 out of 30 days, was a key inclusion criteria. At randomization, patients had to be experiencing at least minimal symptoms of active withdrawal in order to validate a state of physical dependence.

Pivotal studies 2 and 3-1 excluded patients currently taking or having a recent history of prescribed psychotropic, prescription analgesic, anticonvulsant, antihypertensive, antiarrhythmic, antiretroviral, or cholesterol-lowering medications.

Use of buprenorphine or methadone, either at baseline or during treatment, were prohibited in the two pivotal lofexidine studies, both because of initial concerns about the possibility of QT prolongation and to maintain consistent time course and synchronization of the process of withdrawal. Following completion of phase 1 drug-drug interaction studies, which were done in parallel with the pivotal programs, use of buprenorphine and methadone was then intentionally permitted in the

open-label study 3-2 to evaluate a broader safety population where concomitant administration of these medications could be observed.

The demographics here of the subjects studied in the pivotal studies were consistent with the typical epidemiology and treatment presentation patterns representative of the patients we treat in usual clinical practice. The population was generally well balanced across the arms.

The treatment populations in both studies reflected the heterogeneity in the opioid-use patterns indicative of disorder severity. You can see here that heroin was the major opioid used and that many of the patients were injection users. There was some difference between the two studies with a greater proportion of heroin users in study 3-1 compared to study 2, perhaps indicating a greater severity in the populations. But in both studies, there was also representation of patients whose primary opioid was a prescription opioid rather than heroin in those who were non-injection users. Opioid-use patterns were similar across

treatment groups.

Urine drug screening revealed other non-opioid substance use in about half or more of the populations in both studies, again, generally balanced across treatment groups. These most common non-opioid substances were stimulants, cannabis, and benzodiazepines.

Since the two pivotal studies required full and abrupt cessation of short-acting opioids and given the intensity of withdrawal expected in an abrupt withdrawal situation, ethical considerations for placebo-treated patients in an attempt to retain patients in treatment for data collection, a standardized list, shown here, of supportive medications was permitted for PRN use.

These included symptom-specific support medications, such as acetaminophen for pain, zolpedem for insomnia, and Pepto-Bismol for gastrointestinal symptoms, and the full list shown here of medications permitted in studies 2 and 3-1. These medications were made available to all patients on an as-needed basis at the discretion of

the investigator, but any opioid treatment was considered rescue medicine requiring study termination.

The study assessments across the program enabled comprehensive evaluations of efficacy and safety. The short opioid withdrawal scale by Gossop, or SOWS-Gossop, or SOWS-G, was used in both studies and was the co-primary endpoint measure for both pivotal trials, as I will review. In addition to the SOWS-Gossop, we used a number of additional subjective and objective scales for daily assessment of withdrawal syndrome severity and relief associated with the study medication. These additional measures included the objective OOWS, the subjective VAS-E, and MCGI patient and rater scales.

The later studies, 3-1 and 3-2, also collected data on the objectively assessed COWS, the Clinician Opioid Withdrawal Scale, which has become common in clinical practice in more recent years. Safety assessments were planned to characterize the expected product profile as

informed by earlier clinical studies and lofexidine's known mechanism of action. These assessments included frequent collection of vital signs, daily ECGs, and collection of clinical labs and adverse events. Because SOWS-Gossop is the driving outpoint, we'll review this scale in greater detail.

The scale shown here, the SOWS-Gossop, is a shortened version of a historical 32-item scale that covered a broader list of opioid withdrawal symptom attributes. It is a 10-item, patient-reported outcome measure of physical opioid withdrawal symptoms. Some items were eliminated from the original larger scale using prospective methods to determine low loading and others to limit redundancy. The resulting 10-item list was found to correlate well to the more extensive 32-item scale in determining overall severity.

Thus, SOWS-G is considered a validated instrument to assess severity of the overall withdrawal experience. Each item is rated on a Likert scale as none, mild, moderate, or severe

equivalent to point values of 0, 1, 2, or 3. Note that a higher score is indicative of more severe withdrawal symptoms with a theoretical maximum rating of 30. Due to the rapid changes in symptoms and withdrawing patients on a day-by-day basis, that theoretical maximum of 30 points would be rare, as it would require the highest severity rating for all 10 symptoms at any given time.

Observed scores are actually generally expected to be lower even in severe withdrawal cases. This is important to put the scoring scale in perspective. The subjective symptoms of withdrawal are really very individual in terms of which symptoms are most bothersome to each patient. Each may have their own particular pattern of symptom severity, as Dr. Baxter mentioned, but the presence of these symptoms, whether from just a few to even all 10, can cause significant distress to a particular patient. Relief on as little as 2 or 3 of the patient's most bothersome symptoms, although representing a small change score in an instrument like the SOWS-G, can make a meaningful improvement

in a patient's experience.

To illustrate this, here is an actual example from study 2 of a patient on day 2 of the study to illustrate what seemed to be small changes could reflect a huge improvement in an actual patient clinical response. You can see that this patient rated 2 of the items as severe with 3 others related moderate, 3 rated mild, and 2 rated none. This particular rating translates into a total numerical score of 15, and while the number alone may not sound especially severe, actually this is a person who says that he has the highest severity on two very salient symptoms, feeling sick and experiencing insomnia.

If those two were to move down just one category from severe to moderate, that would be a change of 2 points. If they moved down two categories, that would be a change of 4 points, perhaps not much mathematically, but in my experience very clinically impactful. Similarly, if the three moderate symptoms -- stomach cramps, muscular tension, and aches and pains -- moved to

mild, the change would be just 3 points but quite possibly enough to give a distressed intolerant patient enough motivation to stick it out, and getting patients through withdrawal is our goal.

Now let's discuss the endpoints in the pivotal program shown here. Both studies evaluated endpoints which directly support the sponsor's two proposed indications in mitigation of symptoms and facilitation of opioid discontinuation treatment. The endpoints were planned in this way because clinically meaningful reduction in symptom severity is synergistically expected to result in greater retention of patients in withdrawal management. Therefore, subjective relief as reported by patients and completion of withdrawal were both considered important to evaluating the patients' benefits.

Both studies used the SOWS-Gossop to evaluate symptom severity. In study 2, it was evaluated in scaled differences at day 3, and in study 3-1 evaluated by scores across days 1 through 7 in their totality. Both studies used completion

as a co-primary endpoint. Study 2 used time to drop out over 5 days. Study 3-1 used proportion of completers over 7 days.

Opioid-use disorder patients in particular are extremely difficult to retain through completion of opioid withdrawal. This difficulty leads to an expectation of high dropouts in this patient population. Many of these dropouts will leave treatment because they've lost motivation or changed their mind about treatment. However, the successful management of symptoms is the most clinically controllable factor in retaining them. This is why complementary completion endpoints were used to evaluate the benefits of lofexidine in addition to symptom severity endpoints.

This combination of endpoints is important and relevant because the misery of withdrawal is often a deal-breaker for patients and retention through withdrawal is a critical milestone in part of a broader ongoing treatment plan. And now my colleague Dr. Gorodetzky will present the program's efficacy results.

Applicant Presentation - Charles Gorodetzky

DR. GORODETZKY: Good morning. I have been engaged in the conduct and management of clinical research for more than 50 years. I've been directly involved with the lofexidine development program since 2005 during which time I was the principal investigator for the pivotal studies to be presented here. I will present a summary of the pivotal clinical efficacy results from the clinical development program that Dr. Fishman introduced.

This graph shows one of the study 2 co-primary endpoint results, the difference in mean SOWS-Gossop scores on day 3. A lower score indicates less intense withdrawal. The mean scores for the placebo group reflect the expected symptom profile for withdrawal from short-acting opioids. Symptom scores peaked on day 2 and decreased through day 7.

Lofexidine significantly reduced SOWS-Gossop scores on study day 2 and study day 3, which is the primary efficacy endpoint. Scores were similar on days 4 and 5 and overlapping on days 6 and 7 when

both groups were receiving placebo. On days 2 to 4, mean SOWS-Gossop scores differed the most, and that timing is especially clinically meaningful since that is within the most vulnerable window for patient dropout.

Early discontinuations in both groups resulted in missing SOWS-Gossop data. Missing data were conservatively handled using multiple imputation and other statistical methods described in the briefing book. Even after adjusting for missing data, as you can see in this slide that includes the computation adjustment, the efficacy results favor lofexidine.

The other co-primary endpoint in study 2 is time to study discontinuation. Retention was higher with lofexidine treatment compared with placebo beginning on day 1 and continuing throughout the duration of treatment. The prespecified log rank test for the active treatment phase that is through the first assessment on day 5 was statistically significant in favor of lofexidine. By the end of day 2, approximately

50 percent of placebo patients had dropped out.

The median time to study discontinuation was approximately 2 days longer for the lofexidine treatment group compared with the placebo group. Completion rate in study 2 was defined here as patients who completed 5 days of study treatment and discharged on day 6 or later. Completion rates were statistically significantly higher in the lofexidine treatment group compared with the placebo treatment group.

The primary endpoint for study 3-1 was the difference between least squares means for the overall log transform SOWS-Gossop scores from study days 1 through 7. Score patterns in study 3-1 were similar to those in study 2. Statistical differences between lofexidine and placebo treatments were apparent after the first dose on study day 1.

As for study 2, the largest treatment differences were observed on days 2 to 4 when withdrawal symptoms were highest. The least squares mean differences was statistically

significant for both lofexidine treatment groups compared with the placebo group. The p-values for the log scale mean differences are shown in the table insert in the figure.

The by-day T Value is shown beneath the figure. The differences from placebo were mostly highly significant at p less 0.1 through day 4, significant on day 5 at p less than 0.5, and similar on days 6 and 7. SOWS-Gossop scores on days 1 to 4 trended slightly lower, therefore more favorably for lofexidine 3.2-milligram per day compared with lofexidine 2.4-milligram per day treatment.

Also similar to study 2, the retention analysis for study 3.1 showed higher retention in both lofexidine groups compared to placebo. Prespecified Cox regression analyses showed each lofexidine doses to be statistically superior to placebo. The median time to study discontinuation was approximately 2 days longer in the lofexidine treatment groups, and 50 percent of the dropouts in the placebo group occurred by the end of the second

day. Retention was analyzed through the first assessment on day 7. On day 7, completion rates showed higher retention and completion with lofexidine. Based on odds ratio calculated for study 3-1 on day 7, lofexidine patients had approximately a 70 to 85 percent greater odds of completing withdrawal treatment compared to placebo subjects.

The SOWS-Gossop scale, as noted earlier, is a subjective patient-reported outcome. The clinical opioid withdrawal scale, or COWS, contains both subjective and objective measures. The COWS was one of the exploratory measures used in study 3-1. It had not yet been developed at the time that study 2 was conducted. COWS mean score changes are shown on the right. Like the SOWS-Gossop, a lower score indicates less severe withdrawal.

The pattern of COWS scores was similar to that of the SOWS scores peaking on day 2 and decreasing through day 7. Differences between placebo and lofexidine treatments were

statistically significant and favored lofexidine on study days 1 through 5. Similar to these scores, a wide variety of both subjective and objective secondary and exploratory endpoints showed results consistently in favor of lofexidine over placebo.

This slide shows a forest plot comparing a standardized treatment effect for lofexidine versus placebo for the SOWS-Gossop endpoint and 5 secondary endpoints for both pivotal efficacy studies. Adjusting by an estimate of the population standard deviation produces a value at 95 percent confidence limits, which can be viewed across endpoints. Values less than zero indicate an outcome favorable to lofexidine. All of the secondary endpoint results in both studies favored lofexidine. None of the 95 percent confidence limits overlapped the zero line.

The results from study 2 and study 3-1 at 3.2 milligrams, as indicated in the blue diamonds, were similar. However, in study 3-1, which included both lofexidine 3.2- and 2.4-milligram per day, efficacy trends consistently show greater

benefit for the higher 3.2-milligram lofexidine dose.

The primary efficacy endpoint was achieved in both pivotal trials. Results favoring lofexidine were consistent across multiple efficacy measures both subjective and objective. Both doses of lofexidine 2.4 milligram per day and 3.2 milligram per day was significantly more effective than placebo; however, efficacy trends consistently favored the 3.2 milligram per day dose. Lofexidine significantly alleviated withdrawal symptoms compared with placebo, and patients on lofexidine had higher probability of completing discontinuation treatments.

In sum, lofexidine and the efficacy data from the two pivotal studies support the proposed label indications. Dr. Mark Pirner will now present the safety results.

Applicant Presentation - Mark Pirner

DR. PIRNER: Good morning. I'm senior medical director for US WorldMeds, and I was responsible for the NDA clinical modules and

overviews. The lofexidine clinical development program demonstrated a safety profile consistent with both symptoms of opioid withdrawal in the lofexidine drug class. Adverse events related to opioid withdrawal tended to be higher in the placebo group and adverse events related to lofexidine mechanism of action were more prevalent with lofexidine treatment, as might be expected from an alpha-2 agonist.

During my presentation, I will present the foundation for interpreting the safety results and then discuss each topic of special interest.

The studies, as Dr. Fishman presented, were designed to create a robust safety database. Total exposure of lofexidine was sufficient to adequately assess and confirm lofexidine safety. Treatment emergent adverse events were balanced across arms, and as expected, events related to opioid withdrawal were high. Events related to drug mechanism of action were more common with lofexidine. Vital sign analysis revealed expected mean tendencies toward decreased blood pressure and

mean heart rate remained at or above baseline levels.

Outlier analysis demonstrated that with few exceptions, standing systolic blood pressures for orthostatics were 90 millimeters of mercury or higher; in other words, clinically acceptable and consistent with the low incidence of fall, syncope, related SAEs, or discontinuations. The incidence of serious adverse events was low as might be expected with the drug class. Discontinuation rates reflected the beneficial impact of lofexidine on study retention.

We'll also be addressing topics of special interest. Early signals of QTc prolongation were not confirmed in the phase 3 program. Adjustments for reduced drug metabolism and clearance will be recommended in patients with renal or hepatic impairment. I will conclude with a summary of safety experience from the United Kingdom, which is consistent with that seen in our clinical development program.

In our phase 3 studies, which we present

here today, over 900 patients were randomized to lofexidine. This includes patients from the non-pivotal study 1. Nearly half of the patients were treated through day 5, which was the end of the randomized treatment in study 2. Overall, one-third were treated through day 7, which was the end of study 3-1. After day 7, about 10 percent of the patients were enrolled in the open-label extensions.

Throughout my presentation today, green boxes as you see here will be used for emphasis. In this slide, the green box highlights days 2 through 4. As Dr. Gorodetzky showed in the efficacy presentation, the number of patients in study 2 and 3-1 declined precipitously between days 2 and 4 corresponding to days of peak withdrawal symptoms. Treatment emergent adverse events were balanced across arms. As expected, events related to opioid withdrawal were high. Investigators defined non-opioid withdrawal related events as not related to expected symptoms of withdrawal. For example, hypotension and

bradycardia would fit into this category.

A more detailed analysis of specific opioid withdrawal related events, as you see here in the green boxes, demonstrated as expected a trend toward more withdrawal related adverse events in the placebo group, a result consistent with less efficacy. Where not higher, the incidence between placebo and lofexidine were similar except for insomnia in study 3-1.

When we turn to non-opioid withdrawal related events, we see increased incidences of hypotension, bradycardia, dizziness, and sedation as expected with the lofexidine mechanism of action. In study 3-1, incidence rates for orthostatic hypotension, bradycardia, and dizziness were higher than placebo and dose dependent. These events were also higher in studies 3-1 and 3-2 than in study 2 due to protocol differences for reporting vital signs as AEs.

In 3-1 and 3-2, investigators were required to report vital sign changes as adverse events even when there were no clinical symptoms. Even though

we saw increased rates of orthostatic hypotension, bradycardia, and dizziness, we saw little evidence of serious clinical sequelae. In particular, the incidences of fall and syncope were low. There were no events of fall or syncope in the placebo groups. Vital sign analyses were consistent with the low incidence of fall and syncope, and later I will show you the low incidence of serious adverse events or discontinuations related to vital signs.

Central tendency assessment of vital signs demonstrated predictable and dose-dependent reductions in mean-standing blood pressure. Study 2 is shown on the upper left and study 3-1 on the upper right. Solid lines are systolic blood pressure and dotted lines are diastolic. You can see a consistent decrease that starts on day 1 and continues through the treatment period.

Below them, mean-standing heart rate remained close to or above baseline values in both studies. On the left in study 2, after lofexidine was withdrawn on day 6 and 7, mean blood pressure values on the top returned to baseline. Mean heart

rate on the bottom also moved toward placebo. Rebound hypertension did occur and will be covered in the FDA presentation.

To assess the lowest or worst blood pressure change for each patient, we plotted the lowest observed orthostatic systolic blood pressure change for each patient in 3-1. The change from sitting to standing is plotted on the Y-axis. The horizontal line is the zero or no change from sitting to standing. Placebo patients are represented by the gray triangles, lofexidine 2.4-milligram patients are the red circles, and lofexidine 3.2-milligram patients are the blue squares.

As is expected, most patients experienced a drop in blood pressure from sitting to standing. Decreases ranged as high as 70 millimeters of mercury, but this was uncommon and occurred in both lofexidine 2.4 and 3.2-milligram treatment groups. Most patients did not have a decrease more than 40 millimeters of mercury, and decreases clustered between 0 and 40. Also as expected, decreases

occurred least in placebo patients and the greatest in lofexidine patients and reflected a dose-dependent trend.

Here we see the same plot with diagonal lines that show cutoffs for the standing systolic blood pressures that were observed. In other words, patients with orthostatic standing systolic blood pressures below 70 millimeters of mercury or below the bottom line. Most of these were in the 3.2-milligram group. The middle diagonal line is 90 millimeters of mercury.

Here we see that for most patients, the lowest orthostatic standing blood pressure was above 90 millimeters of mercury, which is within normal clinical limits. Dose-dependent trends towards lower blood pressure occurred with lofexidine. Consistent with these results and the analysis of AEs, the incidences of SAEs and discontinuations due to AEs related to vital signs were low. Serious adverse events were infrequent and balanced between treatment groups. We conducted a detailed analysis to characterize these

events.

In study 2, SAEs for severe opioid withdrawal symptoms occurred the most. These were coded as serious when prolonged hospitalization was required to ensure that patients were stable prior to leaving the study sites. The remaining SAE terms in all of the studies occurred in 1 or 2 patients for each event term. Consistent with the lofexidine drug class, there were 3 lofexidine patients reported in study 2 and 2 lofexidine patients in 3-1 with SAEs related to hypotension and bradycardia. There were none in 3-2.

Based on the drug class, there were 4 unexpected SAEs in the lofexidine treatment groups that require further analysis. These were chest pain, suicidal ideation, delusion, and cerebral vascular accident. Chest pain was reported for a 37-year-old white woman who described chest pounding and discomfort associated with hypotension and bradycardia on study day 4. Serial ECGs reviewed by a cardiologist did not suggest cardiovascular pathology.

Suicidal ideation was reported for a 28-year-old white man on study day 28, 18 days after his last dose of lofexidine on study day 7. His past history included ADHD, heroin abuse, and alcohol abuse for 12 years. His Columbia Suicide Severity Rating Scale was negative for suicidal ideation at baseline and during the study. He was hospitalized and the event resolved without sequelae.

A cerebral vascular accident was reported for a 48-year-old African American man on study day 7. He had a 27-year history of tobacco use and past medical history significant for hypertension, hyperlipidemia, congestive heart failure, and vasospastic myocardial infarction. Past cardiac catheterizations were negative for coronary artery disease, but he had a history of poorly treated apical left ventricular thrombus. Brain MRI revealed evidence for a left-middle cerebral artery thrombotic stroke. Transthoracic echocardiogram revealed an apical left ventricular thrombus. The discharge diagnosis was left-sided middle cerebral

artery stroke due to LV thrombus.

Delusion was reported for a 27-year-old white man on study day 10. He received lofexidine 3.2 milligrams per day on days 1 through 7 and 2.4 milligrams per day or lower on days 8 through 14. He had a history of heroin abuse; alcohol abuse; 2 past suicide attempts by overdose to stop pain; a prior psychiatric admission for psychosis; and a history of chronic intermittent psychiatric illness. On study day 10, he reported having paranoid thoughts and anxiety that required psychiatric evaluation. He left against medical advice and was acutely hospitalized, diagnosed with bipolar disorder and psychotic features.

There was one treatment emergent death reported. This occurred in a 34-year-old white woman who died of an accidental, multiple drug, intoxication 3 days after completing 7 days of lofexidine. Her past history included heroin use. Her urine drug screen was positive for opiates. Three days after the last dose of lofexidine, an autopsy showed that she died of severe accidental

multiple drug intoxication, including fentanyl, cocaine, and heroin.

Treatment emergent AEs leading to discontinuation were also balanced between treatment groups. More discontinuations occurred in study 3-1 and 3-2 than study 2 as a result of protocol differences related to vital signs and missed doses. Both 3-1 and 3-2 protocols required discontinuation criteria for repeated missed doses and for categorical vital sign changes independent of whether patients were symptomatic. Study 2 better represents discontinuation events driven by subjective symptoms.

Like the AE and SAE profile, more patients in the placebo group discontinued due to events related to opioid withdrawal consistent with less efficacy. Only a small proportion of patients who experienced orthostatic hypertension, bradycardia, and dizziness discontinued. We conducted a detailed analysis of discontinuations resulting from AEs and lack of efficacy in study 3-1.

Dr. Gorodetzky showed that in study 3-1,

efficacy trends consistently benefited the higher lofexidine dose except completion rates, which were similar between the doses; however, the reasons for discontinuation were different. Adverse events were more common in the high-dose group; lack of efficacy was more common in the low-dose group. Consistent with efficacy and safety results, lack of efficacy was most common with placebo. The higher lofexidine dose may be optimal to retain patients as long as drug class effects can be managed.

Our examination of topics with special interest included early potential QT prolongation signals observed in in vitro hERG and dog studies at lofexidine levels that were substantially higher than those measured in clinical studies. QTc prolongation was also observed in phase 1 normal, healthy volunteers, and these results led to more extensive monitoring in phase 3. Dose adjustments will be recommended for patients with reduced capacity for drug metabolism and for clearance.

In study 3-1, plasma lofexidine levels were

measured and correlated to change in QTc interval. This analysis showed that initial QTc interval increases, seen on the top left, did not exceed 10 milliseconds and occurred at low lofexidine concentrations seen in the table at the bottom. Unexpectedly, after 4 and 7 days, mean QTc intervals decreased below baseline in both lofexidine and placebo groups, while, as seen in the table below, lofexidine plasma concentrations were substantially higher. We can draw two conclusions. First that in withdrawing patients, mean increases in QTc interval were transient and not clinically significant. Second, withdrawal appears to have the predominant effect on QTc interval change in this clinical context.

This plot of the maximum QTc interval change from baseline at any point during study 3-1 is similar in design to the outlier systolic blood pressure plot I showed earlier. As before, change from baseline is plotted on the Y-axis. In this case, most of the QTc interval values increased from baseline, and there is less clear experience

of any substantial dose effect.

In this plot, the diagonal lines delineate the highest QTc values for each patient. Note that almost all maximum values were below 450 milliseconds and not of clinical concern. One patient in the placebo group had a maximum QTc greater than 500 milliseconds. There were none in the lofexidine groups. Lofexidine dose reductions will be recommended for patients with reduced capacity for metabolism or clearance based on renal impairment or hepatic impairment.

We have two sources of UK safety data. The results both demonstrate a similar safety profile to the one established in US WorldMeds clinical program. One source is the pharmacovigilance summary of exposure in spontaneously reported adverse events. The other is a published retrospective survey of more than 1,000 patients treated for withdrawal in both inpatient and community settings. The approved maximum daily dose of lofexidine in the UK is 2.4 milligrams per day.

Approximately 300,000 detoxification treatment courses have been prescribed in the UK based on sales data. Very few spontaneous adverse events have been reported, and of these, the most commonly reported events, including bradycardia and hypotension, are consistent with those with from our clinical development program and the drug class.

The published retrospective survey reviewed data collected on 1,074 opioid-dependent detoxifications conducted from 40 drug dependency units in the UK under the remit of the safety assessment of marketed medicine's guidelines. This survey was observational. It reported approximately 60 percent success rate for detoxification for both inpatient and community settings. Most patients who completed detoxification titrated to a mean dose of 2.2 milligrams per day, and the mean duration of treatment was 10 days. The most frequently recorded adverse events were dry mouth, sedation, hypotension, and dizziness, again in line with our

clinical development program.

Lofexidine safety has been comprehensively studied in three phase 3 studies and one large open-label extension study. Adverse events reflect lack of efficacy in the placebo group and expected drug class effects. The observed incidence of orthostatic hypotension, bradycardia, and dizziness was clinically tolerated with few events of fall, syncope, serious AEs, or discontinuation AEs related to vital signs. The higher lofexidine dose may be optimal with management of drug class effects.

The data suggests that precaution should include hypotension and bradycardia, including concomitant antihypertensive and bradycardic medications and/or underlying cardiovascular disease; rebound hypertension; QT prolongation; dose adjustment for renal or hepatic insufficiency; and caution with concomitant drugs known to call CNS sedation.

To respond to these events appropriately, US WorldMeds plans to develop comprehensive education

materials for healthcare providers, patients, and their caregivers focused on three pillars: appropriate patient selection, the importance of patient counseling, and the need for clinical management. US WorldMeds will produce information that suggest that patient who do not have appropriate supportive care may not be appropriate candidates for lofexidine treatment.

Clinical judgment will be critical to identify safe and appropriate patients and treatment settings. Drs. Baxter and Fishman both referenced the importance of ASAM criteria to triage safe, ambulatory, or residential management. Key patient safety factors include psychological and comorbid conditions, including concomitant medications such as antihypertensive, heart-rate lowering drugs, CNS sedating drugs, or drugs known to prolong QT. Dosing instructions and appropriate precautions must be clearly communicated and understood by both the patient and their care support. For example, patients should be cautioned to remain hydrated and reduce other activity. If

they feel dizzy, they should lie down.

Patients should also be advised what to expect. Lofexidine treatment will mitigate but not completely prevent symptoms of withdrawal. Withdrawal will not be easy, and additional supportive care measures should be clearly advised as needed. Patients and their supportive caregivers should be instructed what to look for and when to call their health providers or when to seek emergency support. Clinical management will include appropriate dose adjustment, including dose reduction guidelines. Risk related precautions and warnings will be clearly defined and presented in our label. These educational materials will be designed to help ensure that lofexidine can be used both effectively and safely in the withdrawal process.

Next, Dr. Kosten will present his clinical perspective.

Applicant Presentation - Thomas Kosten

DR. KOSTEN: Good morning. I'm the Waggoner chair and professor of psychiatry with 35 years

experience in treating opioid dependence and withdrawal. I've been a leader in several major clinical organizations and addiction treatment, including the American Academy of Addiction Psychiatry and the College on the Problems of Drug Dependence. I've also directed medication development programs with the Department of Defense, the VA, the NIH, and various pharmaceutical companies.

My role today is to provide a clinical perspective on the potential role of lofexidine and opioid withdrawal management. No matter what path patients take to physical dependence on opiates, they will experience opioid withdrawal upon cessation of opioid use. As you've heard from my colleagues earlier in the presentation, patients fear opioid withdrawal. The opioid withdrawal syndrome is often so distressing during the initial days of the process that patients abandon their attempt to discontinue opioid use.

The syndrome is characterized by the adrenergic surge causing these intense symptoms, a

barrier that can derail a patient from transitioning to their post-withdrawal treatment plans. We see that appropriate withdrawal management is an essential step in the process. Unfortunately, we have insufficient tools to manage opioid withdrawal today where the major limitations of current therapies are several-fold. Reliance on opioid-based medications comes with concerns about abuse and diversion.

Only methadone is FDA approved for use in withdrawal, but access to these treatments is often compromised due to special licensing required for opioid medications. Other commonly used withdrawal treatment options are used off label, and there's limited standardization of these practices. Further, access to these treatments are often compromised due to special licensing required for opioid medications and the lack of available specialized clinicians and treatment facilities.

Finally, because unapproved treatments are often guided by experience rather than substantial evidence, practice and outcomes are variable.

There's a need for a pharmaceutical intervention that's non-opioid with lowered risk of abuse and diversion, one that is approved and labeled for proper and consistent prescribing, and one that can be used broadly and confidently across physicians.

This intervention needs to be supported by a comprehensive clinical program that has established safety and efficacy in withdrawing patients. These limitations create an unmet need in the management of opioid withdrawal, a need lofexidine has the potential to address.

Lofexidine acts through a well characterized and clinically established mechanism of action. It is an alpha-2 adrenergic agonist that reduces norepinephrine hypersecretion, a root cause of opioid withdrawal symptoms. With no other relevant receptor activity, it is not associated with abuse potential. In addition, lofexidine was studied in a comprehensive development package designed to support an FDA-approved label. This package informs evidence-based dosing recommendations, offers clear precautions, and provides information

on appropriate patient counseling.

In addition, because withdrawal support can be provided by general practitioners, physician extenders, and other non-specialists, it can be used in a variety of treatment settings, including office-based treatment for the appropriate patients with caregiver availability and support systems. It can also be used in underserved geographic areas where access to specialty providers and treatment facilities are not available.

Lofexidine's efficacy assessment is based on subjective and objective measures of opioid withdrawal severity. Both patients and their treatment providers saw improvement in patient comfort level. Lofexidine treated patients also were more likely to complete opioid withdrawal treatment. Finally, lofexidine's safety profile is similar to others with its mechanism of action.

Let's explore how the data we've reviewed translates into a risk-benefit assessment. The most important patient risks are associated with lofexidine's mechanism of action and could be

considered class effects. The events included orthostatic hypotension, dizziness, and potential syncope and falls, but these events were rare and generally mild to moderate.

Patients also experienced sedation in the lofexidine arms, however, sedation was rarely problematic enough to cause study discontinuation. QTc changes were not clinically concerning and were self-limiting. Importantly, no side effects required anything beyond general support of management. They resolved without sequelae and generally did so rapidly by simple dose adjustment.

As Dr. Gorodetzky reported in his presentation, efficacy data showed that lofexidine provided symptom relief and increased the percentage of patients completing withdrawal. The efficacy data in this forest plot further show that lofexidine across multiple measures offers clear and meaningful benefits to patients in mitigating symptoms and providing relief from abrupt withdrawal. Data across all the endpoints demonstrate although both doses are effective, the

3.2-milligram dose outperforms the 2.4-milligram dose in every analysis shown here.

In the final analysis, however, we come back to completion of opioid withdrawal. The lofexidine treated patients had up to 80 percent higher chance of completing treatment compared to placebo. When you look at risk-benefit in this context, you see that lofexidine provides a clear advantage.

We have a one or two-week course of acute treatment with lofexidine. We can summarize the benefits of significantly reducing the severity of opioid withdrawal syndrome. In addition, lofexidine treated patients were more likely to remain in treatment during days where withdrawal severity was greatest -- at days 2 and 3 -- and were more likely to complete opioid withdrawal. In short, lofexidine therapy helps patients successfully overcome the barrier of opioid withdrawal.

Successful opioid withdrawal opens the door to a range of relapse prevention therapies, including residential settings of care and

office-based antagonist therapies. The public health benefits are also substantial in reducing the spread of infectious diseases, reduction in illegal activities, and gain full employment.

The sponsor plans to provide educational support for patients and healthcare providers to optimize lofexidine's benefits and supported safe use. They will also look to work with the FDA to ensure that lofexidine's labeling provides information that patients and prescribers need to optimize its use. Education and labeling are important to guide proper patient selection to support the communication of important information to patients and their caregivers, to manage expectations about lofexidine use during opioid withdrawal, and to equip physicians with the data and recommendations necessary to support clinical judgment calls.

Although, opioid withdrawal is generally not considered life threatening, the inability to move beyond opioid use towards subsequent treatment steps, particularly in addiction patients, can mean

immediate return to dangerous use patterns that result in overdose and death, and which has driven the extensive medical, economic, societal, and criminal consequences that our nation is grappling with today.

Both doses of lofexidine can facilitate withdrawal, but the data presented by Dr. Gorodetzky and Pirner established that there's a potential for greater benefit with the 3.2-milligram dose because there were fewer dropouts related to lack of efficacy. People vote with their feet with this medication. There were some adverse events reported more frequently with the higher dose, but not generally those considered tolerability limiting in patients. And the relatively infrequent cases of tolerability concerns, such events could be easily mitigated by dose reduction, which would preserve the higher benefit for the majority of patients.

Dr. Baxter has clearly articulated the importance of engaging and keeping patients in treatment. In my opinion, making both doses

available gives physicians the greatest opportunity and flexibility to engage and retain their patients through opioid withdrawal. The complexity of the epidemic requires coordinated effort across stakeholders, as well as comprehensive treatment approaches, particularly for patients struggling use this order.

Successful withdrawal management is an important part of holistic treatment strategy for all opioid-dependent patients. When we put lofexidine's risk-benefit profile in the context of medical need, we see that lofexidine offers and indispensable and indisputable been both to patients and to public health, especially in the context of the risks of failing to do so.

Now Kristen Gullo will come back to end our presentation.

Applicant Presentation - Kristen Gullo

MS. GULLO: To end our presentation, we would like to review our future plans for lofexidine. Our research programs will be focused on two key areas. The first is pediatric opioid

withdrawals. We will be designing programs with the FDA to cover the full pediatric age range. This will include studies to determine appropriate doses in adolescents; trials across the pediatric age range to evaluate safety and efficacy of lofexidine and iatrogenic opioid withdrawal syndrome; and in newborns with intrauterine exposure to opioids.

These programs will be supported by the development of pediatric appropriate formulations of lofexidine and nonclinical studies in appropriately aged animals to characterize safety prior to initiating clinical investigation. Additionally, because our program focused on a scenario of a rough [indiscernible] withdrawal, we will also work with the FDA to design studies evaluating benefits of lofexidine during an opioid taper.

Our plan is to focus that work in an area of highest need and greatest consistency with medical practice, which is an analgesic taper scenario. Our immediate focus, however, will be in supporting

our LUCEMYRA patients to be successful in achieving their withdrawal goals. We will support their success through multiple initiatives. Some of those are featured here on the screen. We will develop specific healthcare provider and patient websites to provide education around opioid withdrawal syndrome and the use of lofexidine.

We will develop tailored tools for patients and their caregivers, including take-home materials. One of those would include, as an example, a what to expect guide about the withdrawal process, how to support themselves getting through that process, and how to use lofexidine appropriately and what to look for.

Another exciting tool that we will be developing as an encouragement is a smartphone application, sending timed motivational messages to the patients as they go through their withdrawal journey and building in additional features like medication compliance tools and other features, which will be designed in collaboration with patients and caregivers and healthcare

professionals.

Finally, we will support these efforts through coordinated healthcare provider education initiatives, and in doing that, we will collaborate with existing medical associations and societies to leverage some of their educational platforms and also to ensure reach to broad communities of physicians to provide awareness and education around opioid withdrawal syndrome and treatment options available to them.

Through all of these materials, we also hope to provide connections to local resources for patients, particularly those with opioid-use disorder where they may need support groups and they may need connection to long-term recovery care options, which they may not be familiar with.

So with that, we'll conclude today's presentation, and we'd like to thank you for your attention. In addition to our presenters you've already heard from today, featured on the screen are additional expert responders with us and include Drs. Bittman, Pergolizzi, Kowey,

Longstreth, and Schoedel. Thank you again.

Clarifying Questions

DR. NARENDRAN: Thank you. We'll now move to clarifying questions. With respect to clarifying questions, I do want to say try to be as concise as possible. Please don't ask multiple questions. That way everybody gets a chance to answer. And try not to engage in a discussion back and forth so that way we can finish it in 15 minutes. Please remember to state your name for the record when you speak, and if you can, address it to a specific presenter.

We'll start with Dr. Jeffrey, who's on the phone, to see if she has any clarifying questions.

DR. JEFFREY: Thank you for the opportunity to ask. This Jessica Jeffrey. I was wondering, [indiscernible - audio] -- 3.2 milligrams -- statistically significantly different?

MS. GULLO: No, they were not. They trended in favor of 3.2, but the study was not sized to evaluate dose differences. And the results when

comparing the two dose groups were not statistically significant.

DR. JEFFREY: Thank you.

DR. NARENDRAN: Next question, Dr. Dunn?

DR. DUNN: Hi. Walter Dunn. This is a question for Dr. Fishman. I had a question about the subject population recruited for the studies. These subjects, were they answering an advertisement to come into these treatment centers specifically for these studies or were they help seeking and then they were offered the option to participate in the studies?

DR. FISHMAN: There was heterogeneity about that across the different sites. Some did advertise. Most also used a conventional flow at the site where I was PI, which was a SUD treatment program. They were recruited through the usual flow of treatment-seeking patients, but there was heterogeneity.

DR. DUNN: And just a brief follow-up question. For patients who are not withdrawing and are still actively using opiates, is it common to

have a baseline score of 2 or higher in these subjective withdrawal scales? So I guess the question is, if you're actively using, are you still going to show up with a score on like the COWS scale, for example?

MS. GULLO: I think it might be helpful to clarify the design a little bit more. So patients during screening would have still been actively using and therefore not in withdrawal. You'll find that when we do our comparisons of, for example, vital signs, we will use our screening data to make comparisons so that it doesn't have any influence over withdrawal.

The majority of patients that entered the study stayed overnight in the clinic because dosing began early, the morning of day 1. And therefore, the opioids were held overnight, and we were trying to ensure, to further verify a state of physical dependence, that subjects were exhibiting minimal signs of opioid withdrawal at the time of randomization. So really, we would have expected just at least some onset of withdrawal because

there had been no opioid use at least overnight, but that was right before dosing.

DR. NARENDRAN: Dr. Pickar?

DR. PICKAR: Dave Pickar here. A couple questions. On the COWS, nice statistical significance, what items improved? The drug addresses the adrenergic hyperactivity of opioid withdrawal; hence, the alpha-2 agonist part, but in the COWS, statistically significant, but what improved? I didn't see individual items. When I say items, less interested statistically and more clinically. What improved?

MS. GULLO: Yes. I'll ask Dr. Gorodetzky to join me at the podium and review that. And just to clarify, we have item analysis on the SOWS, which was the primary endpoint.

DR. PICKAR: Yes, which is fine. Just more informationally, what did it hit? Was it diarrhea, cramps? Was it muscle aches and so forth, any of that?

DR. GORODETZKY: The specific answer is generally it hit everything. They were fairly

balanced across. For example -- and this was similar in the COWS as in the SOWS.

Can I have the slide, please? This slide shows the effect on the various items of the SOWS, and you can see it's fairly balanced across all of those symptoms. Of course, the SOWS in this 10-item actually represents a whole 32-item questionnaire and includes many of the items, which actually would appear in the COWS as well. So the general answer is that it generally hit all of the items approximately the same.

DR. PICKAR: Interestingly enough, heart pounding looks equal to all things. That would be the most adrenergic thing I think. Coldness. Okay. You can do statistics on individual items, which isn't necessary. But I'm just curious. Heart pounding I would think would be the most adrenergic, and it's not.

What is the biggest one? Feeling of coldness? And I don't know the statistics of that.

DR. GORODETZKY: But all of those generally show the same pattern. The scores are somewhat

higher for placebo and they're generally lower for both doses of lofexidine. This is the 3.1 site, where we had both doses 3.2 and 2.4, and generally it followed the pattern, that the 3.2 gave the lower scores than the 2.4, across generally all items. Not precisely obviously, but generally across all items.

DR. PICKAR: Were any of the items predictive of who dropped out? Because one of the key things is to enhance completion rates. Did any of those tell you who drops out?

MS. GULLO: I'll ask Dr. Pirner to join us. I don't believe that we looked at --

DR. PICKAR: Is predictors of --

MS. GULLO: -- item analysis predicting.

DR. PIRNER: We didn't is the short answer, that we didn't look at the specific items and what led -- but what we can say and what we showed you is that lack of efficacy was a key driver to discontinuation relative to in general. But we didn't do a specific --

DR. PICKAR: Less reduction in COWS score or

OWS score; is that it?

DR. PIRNER: Well -- so I hope I answered this.

DR. PICKAR: Sorry? We'll stop.

DR. PIRNER: Well, we can answer that later.

DR. NARENDRAN: They kind have made their point. They just don't have that answer.

I think Dr. Jain next.

DR. JAIN: Hello. Felipe Jain here. In studies 2 and studies 3-1, patients taking psychotropic medications were excluded. In study 3-2, what proportion of patients were taking psychotropics and what sort of side effect profile would one need to worry about in conjunction with other psychotropic medication?

DR. PIRNER: We will get that information for you. I don't think we have it. But in general, the rate of psychotropic use, it was pretty low because patients had to be stable in order to enter the study, meaning that they had to be safe to themselves and safe to other subjects or participants in the study. So we'll have to get

that. In terms of the patients that we know, we didn't have depression, for example, or anxiety, or things like that. Regression analysis didn't identify any particular signals for safety or efficacy.

MS. GULLO: I think it might also be important to clarify that the use of those other drug classes were not driven specifically by safety concerns but more about ensuring appropriate interpretability of efficacy results since we're relying so much on subjective reporting of symptoms, which included -- we need to be able to rely on the patient to not be influenced by anything else and specifically because we wanted patients that were psychiatrically stable, as Dr. Pirner mentioned.

DR. NARENDRAN: Thank you. Next question, Ms. Witczak?

MS. WITCZAK: Kim Witczak. You asked one of my questions, so thank you. The other one, I'm just more curious about the historical, coming from the UK and looking at their dosage, and kind of

more the philosophical reasons behind doing the higher dosage versus the lower when it's already been kind of established in the UK with their profiles.

MS. GULLO: I'm certainly happy to give a little bit more historical perspective. There were early studies done funded by the National Institute on Drug Abuse. One of those studies included -- which Dr. Winchell reviewed, which was an open-label study trying to look for dose selection for later pivotal trials. Although that was an open-label study, what they found was that starting at 1.6 had some efficacy but maybe was not sufficient to really keep people engaged in treatment. So they did explore doses moving up to 2.4, which is the maximum recommended dose in the UK, and then beyond that to 3.2, and even 4.0 milligrams.

What they found was that they saw clear trends in symptom reduction or sign reduction. I think they used multiple measures in that study. The side effects generally were not tolerability

limiting until they got to 4.0 milligrams. Although there is heavy reliance on the UK experience, dose selection in order to guide the UK label was not done by what we would consider modern controlled and adequately powered studies to determine which doses were really the most effective and/or safe. Although the UK label recommends a dose of up to 2.4 milligrams, our understanding is that a broad range of doses are actually used in clinical practice.

DR. NARENDRAN: Next question, Dr. Turner?

DR. TURNER: Hi. Erick Turner with Oregon Health and Science University. I understand that study 1 was not considered a pivotal study, and it wasn't reviewed, and I didn't see it described in any -- well, actually to any extent really in either the package of the FDA or the sponsor's. I wonder if you could provide us with that. I understand it was terminated early because of the efficacy data; the safety monitoring board terminated it. But nevertheless, there might be some helpful efficacy signals in there or perhaps

some safety issues especially since these were methadone treated patients.

MS. GULLO: Well to clarify, study 1, they were not methadone treated patients. Actually, the study design stabilized patients on morphine for 3 days. There was a 3-day morphine lead-in period, and that was an attempt to homogenize the withdrawal experience, and then they were abruptly withdrawn after that 3-day stabilization period.

If I could have slide 1 up. This is just an overview of the study design. So as I described, the 3-day morphine stabilization period randomization to placebo or lofexidine, the treatment period was 5 days with a 1-day taper on the end, and then they received placebo for 2 days, both treatment groups. And the results are very consistent with everything we've reported in the pivotal studies, but not much focus was given to it in our meeting materials because it is not considered pivotal.

One of the big limitations, aside from the stabilization period, what introduced an

unnecessary degree of artificiality in the study design was the reliance on the modified Handelsman [indiscernible] Opiate Withdrawal Scale, which focused primarily on signs of withdrawal as opposed to the patient's subjected report of feeling better.

DR. NARENDRAN: We have three more questions to close. Dr. Brady?

DR. BRADY: Yes. I was wondering if you have any data on changes in the period after lofexidine was withdrawn in the lofexidine patients.

MS. GULLO: Yes. I'll ask Dr. Pirner to join me at the podium.

DR. PIRNER: In study 2, we had day 6 and 7 where lofexidine patients were switched to placebo. We'll get the slides, but the short answer is that safety was generally similar and there weren't a whole lot of signals differently.

DR. BRADY: Was there any rebound hypertension?

DR. PIRNER: There was categorical. As I

showed you, the mean tendency came back to baseline, but in terms of categorical -- slide 3, please. I think FDA will also present this. There were some patients who did have categorical changes or increases from baseline in blood pressure. If you look at the severity, there is relatively few patients who had blood pressure increases greater than 170. There were some more than 140 or 150 and 160 as well. So there were some, but clinically maybe not so important.

DR. NARENDRAN: Next question, Dr. Carroll.

DR. CARROLL: I understand that the side effects are relatively mild and dose dependent, but as I understood it, the argument for the 3.2 versus the 2.4 was based on higher rates of treatment completion. But the rates are very, very modest to begin with, and it looks like it's actually lower in the 3.2 dose than the 2.4 dose.

MS. GULLO: Yes. We understand this is an important topic that you'll be asked to comment on later this afternoon. First, I think I'd like to clarify that in our assessment, study 3-1 clearly

established both doses are safe and effective, but we don't necessarily see this as an issue of 1 dose or the other, and that is part of what we considered in our dosing recommendations.

Essentially, we're recommending that patients be started as the 3.2-milligram dose because of the data that -- if you'll give us just a minute or two, we'll ask Dr. Pirner to review. It's three slides. And we can also ask Dr. Fishman to give us his clinical experience in dosing because he was involved in both study 3-1 where dose flexibility was not an option for physicians and also in study 3-2, where that flexibility was made available to physicians. I think it's helpful to just get his experience actually treating these patients and managing doses.

If I could ask Dr. Pirner and Dr. Fishman.

DR. PIRNER: So you're spot-on that the completion rate was the same, but the reason for discontinuations were different. Slide 1. Just to show one more time, we saw that there was a higher discontinuation rate in the lower dose due to lack

of efficacy and a higher discontinuation rate in the higher dose due to adverse effects.

Slide 3, please. This is going to be a discussion of trade-offs at the end of the day. Here is the discontinuation specific reasons in the 3.1 study by the two different doses. We see higher discontinuations due to bradycardia, hypotension, orthostatic hypotension, albeit generally low in general, but more with the higher dose. But if you go down to the bottom of the list, you see pain, nausea, myalgia at higher discontinuations where it's with the lower dose, so both doses are effective.

Our position is that the trade-off, if there are patients who can benefit from the higher dose and stay longer in the study -- or said another way, if there are patients who got 2.4 and didn't have the option of 3.2, perhaps we could have had more retention in those patients as well, so it becomes a matter of trade-off.

I know Dr. Fishman has a clinical perspective as well.

DR. NARENDRAN: I think that kind of made the point, so I'm going to allow Dr. Proschan to ask his last question.

DR. PIRNER: Thank you.

DR. NARENDRAN: Thank you.

DR. PROSCHAN: Yes, I have multiple, but I'll only ask one. CC-55, it's a little hard to tell what's going on because there are so many points. I'm wondering if you could just show, first, just the placebo and then overlay the 3.2 -- I'm sorry -- yes, the 3.2 dose.

Is it possible to do that?

MS. GULLO: I'm sorry. Can you clarify the request one more time?

DR. PROSCHAN: Yes. I'm just wondering if it's possible to show just the placebo points because they're kind of hidden behind the two groups. I just wanted to see that graph for the placebo group and then overlay the 3.2 dose on top of that.

MS. GULLO: We can see if we can produce a modified look at this figure, and we can let you

know if it's available after the break.

DR. PROSCHAN: Thanks.

DR. NARENDRAN: Thank you. I think we ran 5 minutes over. We can cut our break to 10 minutes and just reconvene at 10:20 for the FDA presentations. Thank you.

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

DR. NARENDRAN: I think we can now go ahead and start. We will now proceed with the FDA presentations starting with Dr. Horn and then Dr. Ren.

FDA Presentation - Pamela Horn

DR. HORN: Good morning. My name is Pamela Horn. I'm a clinical reviewer in the Division of Anesthesia, Analgesia, and Addiction Products, and Dr. Ren and I will be presenting the clinical and statistical review of lofexidine.

First, I'll be talking about the therapeutic context, including the available data on clonidine used in the U.S., the proposed indication, and a brief overview of lofexidine's pharmacokinetic

profile. I'll also introduce the pivotal studies that were conducted in the lofexidine clinical development program, and then turn it over to Dr. Ren to discuss the efficacy results. Then I'll return to cover the safety review of the application and the conclusions.

Here I'm going to go over the proposed strength, the indications, and dosing regimen, and briefly review how the proposed dosing regimen compares to the dosing of BritLofex in the UK. As you've heard from the applicant, lofexidine is manufactured as 0.18-milligram tablets of active moiety, which is equivalent to 0.2 milligrams of the salt form. In my presentation, I'll refer to the doses that are in the salt form, which is 0.2 milligrams.

The applicant has proposed two indications, which I'll comment on further in the next section of my presentation. The proposed dosing regimen calls for taking 4 tablets 4 times a day, and this represents the highest dosing regimen tested in the phase 3 studies that the applicant conducted and is

the only dosing regimen that was tested in two pivotal studies. This daily dose is higher than both the recommended dose in the BritLofex label and in the regimen that was found to being use in clinical practice in the article by Akhurst that was previously noted in the applicant's presentation.

Here are some summary pharmacokinetics for lofexidine. The maximum concentration is reached at 3 yours, and lofexidine is dose proportional over 1, 2, and 3 tablets, and there were no food effect identified. It's metabolized mainly through CYP2D6 with lesser contributions from 1A2 and 2C19. The elimination half-life is 11 to 20 hours, and it's primarily eliminated through the kidneys.

We've heard about physical dependence on opioids a couple of times already this morning, so just briefly, this is an expected response to chronic exposure, and it results in down regulation of endorphins. It occurs both in the setting of elicit use of opioids such as heroin and in the setting of opioid use prescribed by a healthcare

provider. Here is the DSM-5 criteria for opioid withdrawal. It's very similar to what we've already seen in the applicant presentation, and it's very similar to the descriptions of opioid withdrawal in the literature.

An example of some small differences between different sources of description of opioid withdrawal, there are 2015 ASAM national practice guidelines, that rather than including dysphoric moods as the DSM includes, they include anxiety and agitation, and just a reminder that the onset peak and duration of the manifestations of withdrawal depend on the elimination half-life of the opioid.

This is a summary of the current treatment options, which you've already seen in the applicant presentation. I'll just highlight a few things on this slide. In the first row is methadone, and it's the product that has a labeled indication for detoxification treatment, as we've already heard. I'm going to use the term "opioid withdrawal management" through the rest of the presentation, but it's synonymous with that. Methadone's unique

from the other products in the table in that it's restricted from being used in the outpatient setting outside of opioid treatment programs for the management of withdrawal symptoms.

Buprenorphine is another opioid that we've heard about that's widely used for withdrawal management, and unlike methadone, it can be prescribed in an office-based setting but only through certified prescribers. Many patients who require management of opioid withdrawal have opioid-use disorder, and we know that this is a chronic medical condition. It requires long-term treatment, and for many patients for opioid-use disorder, medication-assisted treatment with an opioid is the best long-term treatment option. And for patients that will go on to long-term treatment with methadone or buprenorphine, withdrawal management with these agents is generally used.

That brings us to the third row in the table, which is clonidine. Like lofexidine it's a non-opioid. It's an alpha adrenergic agonist, and it's most often prescribed for hypertension. The

recommended dosing for clonidine for opioid withdrawal management varies in different guidelines and publications, as the applicant's already noted, and it's often titrated based on clinical assessments. It causes hypertension and bradycardia, and it's also well known to cause rebound hypertension upon cessation. Other drugs that are not listed in the table that are used for symptomatic relief and are available for use in the pivotal studies include acetaminophen for pain, simethicone, an aluminum magnesium hydroxide for gastrointestinal symptoms, among others.

Here I'm going to present the findings of outpatient clonidine IR use in the U.S. for managing opioid withdrawal. The Division of Epidemiology conducted a review of drug utilization and found that in a U.S. office-based physician survey database, 75,000 drug use mentions accounting for 3 percent of total mentions for clonidine IR were reported for the ICD-10 code for opioid related disorders. However, this estimate is too low to provide reliable estimates of

national use. To put these numbers in some additional context, there were 5.2 million mentions of buprenorphine for the opioid related disorders code in the same database.

Although data on prescriptions dispensed linked to indication are not available, analysis of U.S. outpatient retail prescription data showed that the total number of prescriptions of clonidine IR tablets dispensed for any indication has remained relatively stable over a 5-year period, from 2013 to 2017, and the available data was limited to outpatient retail pharmacy settings, and thus it does not capture clinics, addiction centers, or hospitals. Therefore, it's very likely underestimates the extent of use of clonidine.

Next, I'm going to talk about the role for non-opioid drugs for withdrawal management. The most recent SAMHSA treatment guidelines note that there is evidence that continued treatment with buprenorphine or methadone is associated with better outcomes than medically supervised withdrawal. This raises the question why would a

provider use a non-opioid to manage withdrawal symptoms?

Here I've listed a few situations that you have already heard from the applicant, for the most part, where a non-opioid could play a role in patient management. First, patients with opioid-use disorder may not be candidates for agonist treatment for personal or medical reasons, or due to lack of availability. They may also be candidates for and choose treatment with an opioid antagonist and can benefit from a non-opioid to manage their withdrawal while they complete an obligatory opioid free period before they can start the antagonist. In the future, there may be other effective non-opioid options for treating opioid-use disorder where a similar sequence of withdrawal management followed by maintenance treatment would be clinically indicated.

Finally, patients with opioid-use disorder taking an agonist for maintenance therapy and patients that develop a physical dependence on opioids while taking them for analgesia could need

or want to discontinue treatment. There could be a role for a non-opioid in managing withdrawal need situations as well. The efficacy data in the current application do not include data for this last set of clinical situations, and this may be an important area that deserves additional study in the postmarketing setting.

Now, I'm going to talk about the proposed indications. The first indication is a claim that lofexidine mitigates the symptoms of opioid withdrawal. Drug indications are for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

Here, the first indication fits this definition, as it is claiming that lofexidine is mitigating a recognized condition, that of opioid withdrawal. To be labeled for an indication, there needs to be substantial evidence of a benefit in the indication being sought. In this case, as you

have heard already, the SOWS-Gossop was used to assess withdrawal symptoms, and we agree with the applicant that this instrument appeared to provide useful information on the withdrawal symptoms that patients experienced in the pivotal studies.

As we will cover in the efficacy portion of the presentation, the differences between active and placebo treatment groups on this measure appeared large enough to be clinically meaningful and supportive of this first indication. However, in the absence of achieving the treatment goal of stopping the use of opioids, there would not be a purpose to using a non-opioid to treat opioid withdrawal symptoms. This brings us to considering the second proposed indication.

Completion of opioid discontinuation treatment is not a disease or condition, and thus it does not fit into the definition of a drug indication as we generally understand and use it. Completing opioid discontinuation is certainly important. It's the reason we would be given this product to help patients manage their withdrawal

symptoms. But should it be an indication?

Patient completion also helps to confirm or place into context the clinical benefit that was measured on the subjective patient-reported outcome instrument, the SOWS-Gossop, and therefore completion was an important outcome to measure and consider. An alternative to including an indication based on patient completion is to include this information in the clinical studies section of the product label, and we will ask the committee to discuss the best approach to conveying the intended use of and benefit of the drug in the product label.

You've heard a description of these studies already, so I'm only going to reiterate a few key aspects of the studies and the reasoning behind the modifications that FDA made to the analyses conducted before turning it over to Dr. Ren. Study 3002 is referred to study 2 in the applicant's materials, and study 3003-1 is referred to as study 3-1.

The studies enrolled similar study

populations of patients with opioid-use disorder that were experiencing withdrawal from short-acting opioids at the beginning of the treatment period. Study 3003-1 had a 2.4-milligram per day treatment arm in addition to the 3.2-milligram treatment arm and placebo arm in both studies. The treatment period for study 3003-1 was 2 days longer than study 3002, which allowed for a longer assessment of efficacy and safety over time. Both studies employed the SOWS-Gossop as the instrument used to assess the primary efficacy outcome, and as you've heard, the primary efficacy analyses of the SOWS-Gossop and the protocol specified analyses of dropout or completion differed between the two studies.

During the development program, one of the gaps identified in the data that had been collected for study 3002 was that the treatment period was only 5 days while the dosing recommendations for BritLofex in the UK that were labeled were for a treatment duration of 7 to 10 days. And as a result, study 3003-1 was designed with a longer

treatment period of 7 days, and the primary efficacy analysis included the efficacy data out to 7 days.

The applicant has presented the prespecified analysis results, and we agree that they are supportive of the efficacy of lofexidine in both studies. The data on the withdrawal symptoms reported, as one would expect from the opioids that subjects were taking prior to study entry -- short-acting opioids, heroin, and prescription opioids that are short acting -- and what is known about the time course of opioid withdrawal, the withdrawal symptoms peaked around day 2 and had dropped off substantially by the end of the treatment period.

We will present the data for the first 5 days of the treatment period for both studies because we think it's useful for you to see the SOWS-Gossop and completion data for both studies over the same period, and because we think that an analysis that captures the symptoms measured on the SOWS-Gossop over several days of the treatment

period is more informative than a single measurement on one day of the treatment period, which was the prespecified primary endpoint in study 3002.

Like the prespecified analysis results, we find these results to be supportive of the efficacy of lofexidine. There was high dropout in both studies. This is not unexpected and has been observed in other similar studies, but it resulted in much missing data. We addressed this by conducting numerous sensitivity analyses to assess the robustness of the findings, and found that these analyses are also supportive of the primary analysis results.

Here is a quick reminder of the SOWS-Gossop before you see the efficacy results. The data that Dr. Ren is going to present is on total SOWS scores, and as you will see, the mean SOWS scores for patients in the pivotal studies were generally in the range of 4 to 13 in the first few days of the treatment period. This instrument has 10 items and a total possible score range of 0 to 30. It

includes many but not all of the withdrawal symptoms that are described in literature and that are used to define opioid withdrawal in the DSM-5.

Now, I'll turn it over to Dr. Ren to go through the rest of the efficacy portion of the presentation.

Applicant Presentation - Yi Ren

DR. REN: Good morning. My name is Yi Ren. I'm the statistical reviewer of this application. I will present the efficacy results, and then Dr. Horn will return to discuss the safety of lofexidine. Here are the topics I'll cover. I'll begin with an overview of the phase 3 studies. I'll present the efficacy results of these studies. I will then discuss the potential impact of missing data on the efficacy findings and will end with a summary of efficacy.

Dr. Horn has already discussed the study designs of these studies. Briefly, study 3002 was a placebo-controlled study with a 5-day treatment phase. Subjects were randomized to either placebo or lofexidine 3.2 milligrams per day. As Dr. Horn

previously mentioned, for both studies, we looked at the efficacy data for the first 5 days instead of the prespecified endpoints. This is because we think it is useful to see the SOWS-Gossop scores and completion data for both studies over the same time period. Therefore, the efficacy endpoints we looked at for both studies were SOWS-Gossop scores from days 1 to 5 and completion status measured by a proportion of completers on day 5.

In this study, the baseline demographics were similar across the treatment groups. The average age of the subjects was 37 years old. Most of the subjects were male, and over half of the subjects were white. The average baseline SOWS-Gossop score, 12, was the same in both treatment groups.

Among all randomized subjects, more subjects in the placebo group discontinued than in the lofexidine group, 73 percent versus 63 percent. I will discuss the impact of missing data later. In both treatment groups, the most frequent dropout reason was subject's request not related to

withdrawal symptoms. As expected, more subjects dropped out the study due to lack of efficacy in the placebo group compared to the lofexidine group, 28 percent versus 13 percent. There were 5 subjects in each treatment group who discontinued due to adverse event.

I will now discuss the primary endpoint and the corresponding efficacy analysis. In the first row, I will present the applicant's primary endpoint and our endpoint of interest. The applicant's prespecified primary endpoint, SOWS-Gossop scores on day 3 was analyzed using an Ancova model, including baseline SOWS-Gossop scores and opioid-dependent severity based on SCID as covariance.

As previously mentioned, we were interested in SOWS-Gossop scores from days 1 to 5. It was analyzed using a mixed model for repeated measures, MMRM for short. The MMRM model included fixed effects for treatment, baseline SOWS-Gossop scores, opioid-dependence severity, study day, and treatment-by-day interaction. For the applicant,

the second primary endpoint was time to dropout during the 5-day treatment phase. Time to dropout between the two treatment groups were compared using a log rank test. Our endpoint completion status on day 5 was compared using a Fisher's exact test.

To handle missing data, the applicant used multiple imputation in the primary analysis. This imputation model included treatment, baseline SOWS-Gossop scores, and opioid-dependence severity. This method assumed missing at random; that is conditional on baseline covariance, the missing SOWS-Gossop scores would be similar to observed value from complete cases in the same treatment group. This approach could potentially attribute a treatment benefit to a subject that discontinued due to lack of efficacy. Therefore, we used a conservative approach where missing data were computed using placebo mean of complete cases on day 2.

This approach assigns a bad outcome regardless of treatment and dropout reason. It

assumed that data were missing not at random. Five imputations were performed. Results of the MMRM model on each of the five imputed data sets were then combined to derive the overall results. Bonferroni-Holm method was used to control the type 1 error for multiple endpoints.

I will now discuss the results of the primary efficacy endpoint analysis. As you have already seen from the applicant, the estimated difference was statistically significant with respect to SOWS-Gossop scores on day 3. The mean score on day 3 was 2.2 points lower in the lofexidine group compared to placebo group. I will now present the results of the SOWS-Gossop scores from days 1 to 5.

This figure demonstrates the results from our analysis of SOWS-Gossop scores during the 5-day treatment phase. Missing data were imputed using multiple imputation with placebo mean on day 2. The estimated mean scores and 95 percent confidence intervals were plotted over time for subjects in the lofexidine and placebo groups. The solid line

represents the lofexidine group and the dotted line represents the placebo group. You can see a clear separation between treatment groups over time, where the mean scores in the placebo group were higher with a peak separation on day 2. As you can see, the results from our analysis of the SOWS-Gossop scores over 5 days was consistent with applicant's. The estimated treatment effect was 2.3, and it was statistically significant.

I will now present the applicant's second primary endpoint, time to dropout, which was measured in 6-hour time quadrant. The subject's retention rate is displayed on the Y-axis. The study day is displayed on the X-axis. The solid line represents the lofexidine group and the dashed line represents placebo.

The number of subjects at risk by treatment group is shown on the bottom for each day. Starting from day 2, there was a clear separation between treatment groups. The log rank test was statistically significant indicating that the lofexidine group has a higher retention rate

through day 5 compared to the placebo group.

Next is our results. Our endpoint was completion status measured by a proportion of completers who completed the 5-day treatment phase and discharged in the first time quadrant of day 6 or later. As you can see, the proportion of completers on day 5 was significantly higher in the lofexidine group compared to the placebo group. Approximately one half of subjects in the lofexidine group completed the treatment phase compared to one-third of subjects in the placebo group. Statistical significance for both primary endpoints was achieved in study 3002. Now let's look at study 3003-1.

Study 3003-1 was a placebo-controlled, dose-ranging study with a 7-day treatment phase. Subjects were randomized to placebo, lofexidine 2.4 milligrams, or lofexidine 3.2 milligrams per day. As with study 3002, we looked at SOWS-Gossop scores from days 1 to 5 rather than days 1 to 7. In this study, the baseline demographics for all randomized subjects were similar across the

treatment groups. The average age of all subjects was 35 years old. Most of the subjects were male and white. The average baseline SOWS-Gossop score, 10, was the same across groups.

This is the applicant's classification of subject disposition. Note that dropout reason classified as other included lack of efficacy and adverse event, so we reclassified these as either lack of efficacy or adverse event. Based on this corrected table, the most common reasons for dropout were lack of efficacy, adverse event, as well as withdrew consent.

There were more subjects on placebo who discontinued from the double-blind treatment phase than those on lofexidine, 72 percent versus 59 and 60 percent. As with study 3002, more subjects on placebo dropped out due to lack of efficacy than subjects on lofexidine, 36 percent versus 23 and 14 percent. However, there were more dropouts due to adverse event in the lofexidine groups than in the placebo group, 7 and 15 percent versus 4 percent. The most common reason for dropout in

the lofexidine high-dose group was withdrew consent, which is 16 percent.

I will now discuss the primary and secondary endpoint in the corresponding efficacy analysis for this study. The applicant's prespecified primary endpoint, SOWS-Gossop scores from days 17 to 7, was log transformed and analyzed using MMRM model with fixed effects for treatment, baseline SOWS-Gossop scores, sex, study day, and treatment-by-day interaction. We used the same MMRM model for our endpoint and SOWS-Gossop scores from days 1 to 5.

The applicant's secondary endpoint was completion status on day 7 defined as subjects who received at least 1 dose of study medication on day 7 and completed the post-dose assessment on day 7. It was analyzed using logistic regression model with treatment and sex. To be consistent with the previous study, we used a Fisher's exact test to compare the completion status on day 5 between the placebo group and each of the lofexidine groups.

In the applicant's primary efficacy analysis

of study 3003-1, missing data were imputed using a control-based pattern mixture model with multiple imputation. This model assumed that conditional on [indiscernible], subjects who discontinued will have a response similar to subjects in the placebo group that remain in the study. While this may be reasonable, we are still concerned that a good outcome may be attributed to subjects that discontinued due to lack of efficacy or adverse event.

As in study 3002, we used a multiple imputation approach where missing data were imputed using placebo mean of complete cases on day 2. The same number of imputations were performed as applicant. Results of the MMRM analysis on each of the 20 imputed data sets were then combined to derive the overall results. To control for multiplicity, a sequential testing procedure was used, first carried out for the primary endpoint followed by the secondary endpoint. The sequence for each endpoint consisted of a comparison between lofexidine high dose and placebo followed by a

comparison between lofexidine low dose and placebo.

The applicant's results of the primary analysis demonstrated a statistically significant difference with respect to SOWS-Gossop scores from days 1 to 7 between placebo and each of the lofexidine groups.

Next, I'll present our results of the SOWS-Gossop scores from days 1 to 5. As in the previous study, the results from our analysis of SOWS-Gossop scores showed a similar pattern over the first 5 days. The estimated mean scores and 95 percent confidence intervals were plotted over time for subjects in each treatment group. The solid line represents lofexidine high-dose group, the dotted line represents low-dose group, and the dashed line represents placebo. There was a clear separation over time between placebo and each of the lofexidine groups, where the mean scores in the placebo group were higher with a peak separation on day 2, however, the gap between 2-dose groups was minimal and confidence intervals overlapped.

Using the log transform data, our

conclusions were consistent with the applicant's. There was a statistically significant treatment effect in favor of lofexidine. On average, subjects on lofexidine had lower SOWS-Gossop scores compared to subjects on placebo.

The completion status for subjects who completed the 7-day treatment phase was shown by treatment group. Approximately 40 percent of subjects in the lofexidine group completed the treatment phase compared to 28 percent of subjects in the placebo group. As you can see, the odds of having subjects complete the 7-day treatment phase was significantly higher in any of the lofexidine groups compared to the placebo group, while the odds ratio in the high-dose group is slightly smaller than the low-dose group.

Similarly, our results for completion status on day 5 were consistent with applicant's. The proportion of completers was significantly higher in any of the lofexidine groups compared to the placebo group. Approximately one-half in the lofexidine group completed the first 5 days

compared to one-third of subjects in the placebo group.

As discussed, there was substantial dropout in both studies. Around two-thirds of subjects withdrew from the study early, and this was not unexpected, therefore, we explored the impact of missing data during the review. Compared to subjects on placebo, more subjects on lofexidine completed 5 days of opioid discontinuation, 33 percent versus 49 percent in the first study, and 32 percent versus 46 percent in the second study.

Among those completers, consistent results were found across studies that in terms of withdrawal symptoms during the 5-day treatment phase, subjects treated with lofexidine had greater improvement on SOWS-Gossop scores compared to those treated with placebo. Because there were more completers on the lofexidine groups and their SOWS-Gossop scores were lower than placebo, we think these results represents a drug benefit even with the large amount of missing data. However, we

conducted several sensitivity analyses, including complete case analysis, multiple imputation assuming missing not at random, and continuous responder curves. The results from these analyses were consistent and supported the findings of the primary efficacy analyses.

I'll now finish with a summary of efficacy findings. In studies 3002 and 3003-1, there was evidence of efficacy of lofexidine with respect to the primary and secondary efficacy endpoints. Both doses of lofexidine mitigated the withdrawal symptoms and facilitated the completion of opioid discontinuation treatment compared to placebo. In study 3003-1, there was no statistically significant difference between doses of lofexidine.

This concludes my presentation of efficacy results. Now I will turn the podium back to Dr. Horn to discuss the safety findings.

Applicant Presentation - Pamela Horn

DR. HORN: Thank you, Dr. Ren.

You've heard an overview of the product, the therapeutic context, and the efficacy, and now I'm

going to move on to the safety portion of the presentation.

To talk about the different pools of safety data first before I present the results, I'm going to talk about the safety experience in the overall development program; the safety findings in specific studies, especially study 3003-1, which was the only one that had the 2 doses in the same study for lofexidine; and then I'm going to talk about the safety findings in the controlled period of phase 3 studies and the safety findings in all of the phase 3 studies.

When I refer to the controlled period of the phase 3 studies, this is the safety data that comes from the controlled period of studies 3002 and 3003-1, which were the studies I considered pivotal and that were the subject of the efficacy presentation, as well as study 3001, which you heard a little bit about after the applicant's presentation. It was a pilot study that the applicant conducted before study 3002 and 3003-1. It had that morphine stabilization phase. That

study was small. It was randomized, double-blind, and placebo controlled, and subjects were assigned to either 3.2 milligrams per day of lofexidine or placebo. When I refer to all phase 3 studies, I'm referring to the three studies I just talked about as well as 3003-2, which was the open-label safety study where subjects received 3.2 milligrams of lofexidine for up to 2 weeks.

This slide summarizes the exposure in the development program. The total number, 1,276 in the top row of the table, includes all subjects from clinical pharmacology and clinical studies. On the first row of the table is the number of subjects exposed in controlled studies. The next row below that adds in subjects in the 3.2-milligram group that were in an open-label period of a phase 3 study, and then the subsequent rows show subjects that had at least 1, 2, 3, 5, 7, 10, and 14 days of dosing. And as you can see, there were very few subjects exposed to lofexidine beyond 7 days in the development program.

This slide is presenting data you haven't

seen yet today. It's the exposure by mean number of days and mean average daily dose. You can see in the upper half of the figure that the mean number of days of exposure during the control period of the phase 3 studies was around 4 days for all treatments, and the total treatment period in these studies was 5 to 7 days. Because of the differences in the duration of the treatment period and the treatment arms between the phase 3 studies, comparisons between the groups and mean days of exposure aren't really useful, but you can get a sense of how long, on average, subjects were exposed.

On the bottom half of the figure is the mean average daily dose received by lofexidine dose assigned. Both the 2.4-milligram and 3.2-milligram group received less than the total assigned dose on average with a mean average dose for the 2.4-milligram group of 1.9 milligrams per day, and a mean average dose for the 3.2-milligram group of 2.5 milligrams per day. These averages are calculated for days that subjects received a dose

of the study drug and had not dropped out. These lower daily doses are mainly due to doses being held for prespecified vital sign criteria and to a lesser extent due to other adverse events and subject refusal of doses.

This is the beginning of the portion of my presentation on the major safety findings. We've already seen this in the applicant's presentation, but this patient died of an overdose 3 days after completing the entire treatment period. I just highlight it because it illustrates that there is this major risk for patients with opioid-use disorder once they've completed discontinuation, and it really highlights for me the importance of ongoing engagement and treatment for these patients once they've finished opioid discontinuation.

Here is just a brief summary of the nonfatal serious adverse events. As it happened, no subjects that were assigned to the 2.4-milligram group in study 3003-1 had a serious adverse event and around 1 percent of subjects in the 3.2-milligram treatment groups had syncope and

bradycardia. Half a percent had hypotension. For the serious adverse events of bradycardia and hypotension, they were classified as serious because the patients were hospitalized for stabilization of their vital signs.

An example of one of the subjects classified as having a serious adverse event of bradycardia and hypotension while receiving the 3.2-milligram dose was a 40-year-old woman. She also had chest discomfort. Her blood pressure went as low as 75 over 53 and her heart rate was as low as 46 beats per minute. She was discontinued after missing 5 doses of study medication, which was one of the criteria for study discontinuation, and that was on study day 4. She had normalization of her vital signs and no sequelae.

Another example of a patient who had a serious adverse event was a 25-year-old woman who fainted upon standing on study day 5, had a pulse that also happened to be as low as 46 beats per minute, and discontinued after missing 5 doses of study medication. You've already heard about there

was one stroke and one manic episode that were classified as serious in the open-label study.

These are the adverse events that led to discontinuation in the controlled period of all the phase 3 studies. We've seen this data in the applicant presentation. I'll just highlight that hypotension, bradycardia, dizziness, orthostatic hypotension, and syncope were highest in the lofexidine groups. For hypotension, bradycardia, and syncope, they were higher in the 3.2-milligram group. The other thing I will point out is that diarrhea, nausea, and vomiting, which are clearly symptoms of opioid withdrawal, were higher in the placebo groups.

This slide you've already seen as well in the applicant presentation. I'll just reiterate that the discontinuations in study 3003-1 were higher in the 3.2-milligram group than the 2.4-milligram group, in particular, bradycardia, hypotension, orthostatic hypotension, insomnolence, and syncope.

This is a slide that you haven't seen yet.

These were the doses that were withheld in study 3003-1. The protocol-specified criteria for holding doses is in the footnote, so you can see what these criteria were. Only 7 percent of subjects had doses held in the placebo group, while 35 percent of subjects had doses held in the 2.4-milligram group and 44 percent had doses held in the 3.2-milligram group.

The incidence of doses being held because the subjects refused them was similar between groups, but the criteria for which there was a difference in incidence in dose holds between the 2.4-milligram and 3.2-milligram groups were heart rate, symptomatic hypotension or bradycardia, and orthostasis. So I just want to highlight it was symptomatic hypotension or bradycardia.

Now, I'll move on to summarizing treatment emergent adverse events that were more common in the lofexidine groups than the placebo group. I'm presenting data from study 3003-1, alone. The most common adverse event, insomnia is also a symptom of opioid withdrawal. It occurred in around half the

patients in all treatment groups. The next adverse events occurred at a higher incidence in the active treatment groups than the placebo group, and this is consistent with the summarized data on serious adverse events, discontinuations, and dose holds that we've already seen.

Also consistent with data we have already seen, the difference in incidence between doses of lofexidine is for orthostatic hypotension, bradycardia, and dizziness, but not hypotension. In addition to the more frequently observed adverse events, tinnitus and syncope appeared to be related to lofexidine as well, based on these data.

Now I'll move on to vital signs. Consistent with what was observed in the adverse event data and what's know about lofexidine and its mechanism of action, subjects exposed to lofexidine experienced a decrease in systolic blood pressure of about 10 millimeters of mercury and a decrease of 4 beats per minute in resting heart rate below baseline. Vital sign values defined as potentially clinically significant occurred with a greater

incidence in the 3.2-milligram treated subjects than the 2.4-milligram treated subjects.

Two of the phase 3 studies included an evaluation of rebound hypertension. That would be study 3001 and 3002. In one of them, lofexidine 3.2 milligrams per day was tapered for 2 days, and in the other, it was stopped without a taper. That's the only evaluation of rebound hypertension in the program. In both studies, a little less than half the subjects had rebound hypertension, and it peaked at day 2 after stopping lofexidine.

The applicant put up a slide that categorized the level of rebound hypertension by a systolic blood pressure at the end during the questions of their presentation, so I'll just remind you that on that slide, 10 percent of subjects that received lofexidine had a systolic blood pressure of 170 or greater and an increase of at least 20 millimeters of mercury above baseline on day 2 after stopping the lofexidine.

When I compared the two different approaches, the data on blood pressure between the

two different approaches, either a 2-day taper or no taper at all, there didn't appear to be a difference in the occurrence of severity or of rebound between the two discontinuation approaches. There is no data on the 2.4-milligram per day dose to evaluate. This was all on the 3.2-milligram per day dose.

While the incidence of adverse events of hypotension didn't differ between the two dose groups in study 3003-1, the incidence of clinically significant low blood pressure values defined by the applicant was higher in the 3.2-milligram treated subjects than the 2.4-milligram treated subjects. You can see on the first row and on the second row. Then as we've already seen and heard on the summary of major safety findings, there were clinically significant events of bradycardia in both lofexidine dose groups, but the definition used in this table for clinically significant bradycardia didn't capture these and appeared to be too restrictive to capture these.

This is also the first time that you're

seeing today anything about the laboratory values. In the laboratory value data, there was a higher incidence in shifts to modest increases in prothrombin time and in AST and ALT elevations in the lofexidine treated subjects compared to the placebo treated subjects, and that does suggest a drug effect. The changes observed were in very few subjects, and they did not appear to be related to any clinically significant events in the program.

Now I'll cover the cardiac electrophysiology briefly. The conclusions of the review from our disciplinary review team of the available data are summarized here. First, lofexidine does prolong the QTc interval. The effect measured in a pilot QTc effect study of single doses was a maximum mean change from baseline of around 14 milliseconds. In study 3003-1, there was a maximum mean change of 7 milliseconds for the 2.4-milligram group and 9 milliseconds for the 3.2-milligram group, so the data do not appear to represent a dose response between the 2.4-milligram and 3.2-milligram regimens from that study.

There were no cases of torsades de pointes in the development program reported, but in the postmarket setting, there has been one torsades de pointes case in a patient that had received lofexidine in the UK. There are also some data on co-administration of lofexidine with methadone, and when the 3.2-milligram per day regimen was co-administered with methadone in methadone-maintained patients, there was a maximum mean increase of 9 milliseconds over the methadone-only baseline. In the literature, there is a report of three cases of clinically significant QTc prolongation in subjects that received lofexidine co-administered with methadone.

In conclusion, there is evidence that lofexidine mitigates the symptoms of opioid withdrawal, and that the benefit lofexidine provides at both doses studied appeared to be clinically meaningful. With respect to the risks of lofexidine, the main risks are hypotension, bradycardia, and syncope. These risks are higher with the 3.2-milligram dosing regimen than the

294-milligram dosing regimen, and the additional risk that's conveyed by the 3.2-milligram dosing regimen appears to be clinically important. Thank you for your attention.

Clarifying Questions

DR. NARENDRAN: We can move to clarifying questions. Are there clarifying questions for the FDA? Please remember to state your name for the record before you speak. Dr. Jeffrey, we'll start with you because you're on the phone.

(No response.)

DR. NARENDRAN: Dr. Jeffrey?

DR. JEFFREY: Yes. Hi. Jessica Jeffrey from UCLA. I was wondering if we could take a look at the difference in dropout rates by any subanalyses and side effects by subanalyses such as gender, age, or ethnicity.

DR. NARENDRAN: I think she's wondering if there's data by gender, age, or ethnicity, subanalysis of dropout.

DR. HORN: This is Dr. Horn. Do you want it for safety and efficacy? Is that what I heard?

Are you interested in both?

DR. JEFFREY: Yes.

DR. REN: This is Yi Ren, the statistical reviewer. I think for efficacy, we didn't see statistically significant difference across subgroups.

DR. NARENDRAN: I think she's asking about dropout. Is that correct?

DR. JEFFREY: Yes, dropout and safety.

DR. NARENDRAN: Dropouts and safety.

DR. HORN: I'll answer that part. Yes, there was more significant hypotension and other vital sign changes in women. That was the thing that stood out to me the most when I looked at the subgroup analyses of the safety data, and it did translate into some -- I can't say for certain that it was actually discontinuation rates, but there were differences in the vital sign data for women, more clinically significant decreases in blood pressure and heart rate for women.

DR. HERTZ: This is Dr. Hertz. Does the applicant have that data broken out, dropout rates

by demographic subgroup?

MS. GULLO: We have done subgroup analyses for completion status, if that would be helpful. Dr. Pirner?

DR. PIRNER: Sure. Let's go to slide 2, please. In general, our subgroup analysis, we didn't identify any subgroups that had statistically significant differences. There were trends, but then, as you can see on this slide, there was also wide variability for all the different measures. We did note that in women, there was some higher levels of plasma, lofexidine, partly due to size, is what we expect. But again, that did not reach the level where we recommend any dose adjustments.

So I guess the short answer is we didn't see significant differences in completion rate, or efficacy endpoints, or safety relative to the subgroups that we analyzed.

MS. GULLO: Can I add one more thing?

DR. NARENDRAN: Sure.

MS. GULLO: If you want to see the actual

incidence rates, on page 73 of the background document, I've got the differences by gender, sex.

DR. NARENDRAN: Next question, Dr. Jain?

DR. JAIN: Felipe Jain. Following up on Dr. Jeffrey's question, it sounds like both of the non-fatal severe adverse events as well as the fatal adverse event occurred in women taking the 3.2-milligram dose. Looking at the table on page -- it looked like 64 women received the 3.2-milligram dose. So are we looking at a rate of approximately 3 percent of serious adverse effects in women on the 3.2-milligram dose?

DR. NARENDRAN: What was the slide number you mentioned?

DR. HERTZ: Can we try slide 26? This is Dr. Hertz. Slide 26 of the FDA presentation.

DR. JAIN: And that's exactly right, 26.

DR. NARENDRAN: Dr. Horn, do you want to comment?

DR. HORN: I would have to calculate it. It's not something that I've calculated, the serious adverse event incidence for just females.

It's something that we'll look at.

DR. NARENDRAN: Next question, Dr. Dunn?

DR. DUNN: Hi. Walter Dunn. One of your conclusions was that the risk of hypotension, bradycardia, syncope between the two doses was clinically significant. Did that translate into a statistically significant dropout rate between the two doses due to adverse events presumably resulting from the medication?

DR. HORN: Well, we generally don't calculate a statistical significant value. We generally don't calculate it to look at statistical significance when we're looking at safety because none of it is prespecified, and there's an infinite number of analyses that we could do. But I think that I view it as clinically significant.

I acknowledge what the applicant noted that there were some more stringent discontinuation criteria for study 3003-1, which was the only one with the two-dose levels. However, when I looked at things like doses held, when I looked at the symptomatic hypotension and bradycardia, I still

observed a difference between the groups that I thought I were meaningful, clinically meaningful.

DR. WINCHELL: If I might -- this is Dr. Winchell -- I would also point out that one difference between the two studies is that the levels of withdrawal were different. It doesn't seem surprising that people with lower withdrawal to start with would be more sensitive to the cardiovascular effects and then perhaps more likely to meet discontinuation criteria.

DR. NARENDRAN: Dr. Proschan?

DR. PROSCHAN: I actually have a big problem with that forest plot that was just shown a few minutes ago, but I'll reserve that for further comment later. I just wanted to ask if the FDA did any sensitivity analyses where you imputed conservatively, as you did with the placebo mean on day 2, and then just treated that as an actual observation rather than using multiple imputation to account for the fact that the variance is affected.

The reason I asked that is that it's know if

you do something conservative, like you impute the opposite arm value, but then you take into account the variance by doing that, it's actually completely equivalent to throwing out the missing data. So what seems like it would be conservative is actually not conservative.

MR. PETULLO: We had many discussions of clinical and how to impute the missing data. Yes, there was a lot of it. It was discussions on -- I'm sorry, David Petullo, FDA -- how should we impute that missing data. I think in these cases, typically if we say a patient discontinues, they had a bad outcome. I don't think that's necessarily the case here, especially for patients that discontinued on day 4 or 5. They may have been doing okay.

We couldn't quite come to an agreement with clinical on how we should impute this, so for this analysis, we did what we did. We used the highest score on day 2 for patients that dropped out, and there was still a significant treatment effect.

DR. PROSCHAN: That was with the multiple

imputation, though.

MR. PETULLO: Correct.

DR. PROSCHAN: Right. I'm asking whether you did any kind of sensitivity analyses where you just impute that value, treat it as an actual value and do a test without multiple imputation.

MR. PETULLO: I'm not sure that we didn't do it, just putting one score and analyzing, not doing the multiple imputation. We can look into that and see what that is.

DR. NARENDRAN: Next question, Dr. Turner?

DR. TURNER: My question was about the QTc corrections, if you could give us some background on the choice for you to reach a correction. And the rationale is because of lowering a heart rate and the way it corrects for it, and does it make a difference if you -- the Bazett's correction is more a standard. A typical EKG in the clinical world will just say QTc, and it turns out to be Bazett's. So I'm just thinking about the translation of the clinical world.

Then a related question about QTc, that

cloud of points I found hard to tell what's going on, wondering if there is a graph of simply the mean QTc increased change from baseline for the different drug groups.

DR. HORN: I'm going to let the sponsor answer that.

MS. GULLO: Just to clarify, this is in phase 3, the phase 3 QTc changes?

DR. TURNER: Yes.

MS. GULLO: Dr. Pirner, if you could join me? We can show the slide that shows mean QTc change from baseline in the withdrawing patients.

DR. PIRNER: Thanks. Slide 1, please. No, I'm sorry. Slide 2. Slide 1 is fine. That just showed completers. I wanted to show all of the patients available. Seen here is the mean QTc using Fridericia correction on days 1, 7, 8, and 14 for those patients who went into the open label.

DR. TURNER: And that other question about the Fridericia versus other corrections?

DR. KOWEY: Hi. I'm Peter Kowey. I'm a cardiac physiologist from Philadelphia, and I have

the same thing. I was paid as a consultant to be here for my time, so that you know that. Your question is very on point because we would anticipate with a drug of this class that there would be major autonomic changes associated with its use. Not only is that translated to heart rate changes; it really does have a very profound physiologic effect. And that thing that you saw where the QTc actually came down at higher concentrations, it probably reflects autonomic changes.

The direct answer to your question is Fridericia is about as good as you're going to do in an out-of-the-box correction formula. You can use more sophisticated individual corrections. Bazett's would be much more confounded, even though it's a more conventional approach.

What you saw here, all the way through the clinical development program, from phase 1 all the way through phase 3, is a relatively consistent effect on QTc that was modest and not large in any of the patient groups that they studied. It was

what you might have expected from a drug -- through the clinical development, what you would have expected based on its early phase 1 findings, so I think the data are very consistent. But your point about the question is Fridericia is probably about as good as you're going to get for this data set.

DR. TURNER: It's good for what?

[Inaudible - off mic.]

DR. KOWEY: No, good for the better, and taking into account the profound heart rate changes, as you saw on many of the graphs, that this drug causes.

DR. NARENDRAN: Next question, Ms. Witczak?

MS. WITCZAK: Kim Witczak. I guess on slide number 10, you talk about the facilitation, not a disease or condition. Help me understand that, because I know that this is part of that whole new breakthrough therapy. For an unmet need, we only have one clinical trial. Is this a high enough number of people that you would like to see? I also look at this as it doesn't seem like these studies are all replicated, which is more typical

of an FDA approval in the past.

So I'm just curious. I know I've thrown a bunch of questions there at you, but just understanding the not a disease, and if that's part of that whole breakthrough therapy, that it's an unmet condition, and that's why we're able to do one study that doesn't necessarily have to be replicated, although we have indifference between the two, 2 and 3.1 And again, is that number of total people in this study enough? Because it's a big problem we have.

DR. HORN: So just to clarify, you're saying that only one study included a 2.4-milligram dose arm? Is that what you're referring to when you say there was only one study?

MS. WITCZAK: Yes. And just the idea that we're not really doing the replication, and I feel like we're using this whole new kind of FDA approval, using breakthrough therapy with just one clinical trial -- or the number of people in the clinical trial.

DR. HERTZ: I think you're mixing a few

things. This is Sharon Hertz. The breakthrough therapy designation and the use of one or multiple clinical trials are not directly related. Here, what we're trying to do is take a look at the available studies and determine what we have that provides sufficient evidence for us to feel confident in understanding efficacy, and that would be whether it's replicated or not. Then separate from that would be whether or not the safety database is sufficiently large to adequately characterize safety.

So with regard to efficacy, this happens from time to time where the dose that is the focus for efficacy may not be the only dose that we end up interested in and then we have to look at the available date for other doses, be they higher or lower. So here we've done a number of analyses to look at not just the assigned randomization dose, but the actual amount of drug that was delivered to those assigned groups.

I don't recall the slide number, but you can see that, in fact, because of a variety of factors

of withholding dose, a fair number of subjects -- slide 41 of FDA -- a fair number of patients actually, even overall, received less than the maximum randomized dose resulting in this mean of much lower than 3.2 in that treatment group. So when we're thinking about study dose, and when we're thinking about efficacy, we actually look beyond what the randomization would have suggested in this case. So that's why we're contemplating whether the 2.4 may be preferable based on a variety of things, whether or not the efficacy is adequate and whether or not the safety is more or less supportive.

Dr. Winchell?

DR. WINCHELL: As a point of clarification, this development program has not received a breakthrough designation, so does that help?

MS. WITCZAK: [Inaudible - off mic.] I had read it somewhere --

DR. WINCHELL: I think what you're thinking of is a fast-track designation.

MS. WITCZAK: Okay.

DR. WINCHELL: If you would like me to explain the reasoning behind that, I can, or if that takes your question away, we can stop there.

MS. WITCZAK: [Inaudible - off mic.]

MS. BHATT: Turn your mic on, please.

MS. WITCZAK: Yes. I think that was the -- I saw it as breakthrough. But I still think -- and I know you don't do comparative, but I'm just also looking at clonidine. Have you ever looked at those in a similar -- looking back at what is currently being used off label? Has that ever been even tried to come forward for an application or no? Again, another question.

DR. HERTZ: So we don't have off-label use of lofexidine per se in any extent here because it's not approved for anything --

MS. WITCZAK: No, the other drug.

DR. HERTZ: But when we look at clonidine -- I mean, we are aware of the use of this class of drug in this setting. So when we're looking at an application for something novel, we look at the manner in which it's novel, how we

think about everything in the setting for managing the proposed indication. But we don't in this case rely -- we're not relying on efficacy of clonidine. We're aware of the use of clonidine in providing context for understanding the indication, but there's no reference to data from clonidine that are being used to support this indication.

There are circumstances in which applicants may refer to other drugs of similar class, but there's a process that's involved that was not done for this application.

DR. NARENDRAN: Next question, Dr. Brady?

DR. BRADY: I'm still concerned about what looks like there may be more serious adverse events, in particular bradycardia or hypotension in females. I think it may just be that the numbers are too small to make that reach significance, but that could be related to body weight, and I'm wondering -- I thought I saw some analysis in the briefing book of body weight.

DR. HORN: Yes, there is.

DR. BRADY: Can we look at that?

DR. HORN: We'll get the page for you, yes.

DR. HERTZ: But I do want to talk about the question of doing comparisons with statistical analyses for safety data. That's a concept that it can be done. But typically, that needs to be in a setting in which the study's powered for specific safety concerns, and none of that was done here. So in attempt to really do a statistical analysis of what really amounts to a very small number of people with different adverse events I think is asking an awful lot of not a gigantic safety database.

Also, in this context, we consider the safety descriptive. It's not about if it reaches a statistical significance, where sometimes that's necessary for other purposes. Here we're just looking at the trends. We're looking at the differences from placebo. And what's nice is that in some of these data, we have placebo and then 2 doses. So we're just looking at it in that more qualitative sense.

DR. HORN: But to respond to the issue of

body weight and the sex, it does appear that that is part of the reason that the females had more bradycardia and hypotension. I looked at that and put it in the background document on page 74 and 75, so it does appear that body weight is contributing to that effect in sex.

DR. NARENDRAN: I have a question. It sounds like both pivotal trials are done in inpatient setting, the starting and the monitoring. Are you concerned about the broader applicability of how this would go forward, mostly like an outpatient setting? It's not going to have this level of monitoring.

DR. HORN: Yes. That is something that we've thought about. These patients are not going to have nearly as much monitoring. If they're having symptoms, they are going to need to be instructed as to what to do. There is some of the open-label data that the applicant mentioned where they were being treated as outpatients, and the safety experience appear to be quite similar when I reviewed that.

DR. NARENDRAN: Any other questions?

DR. WINCHELL: We do anticipate a need for some patient oriented materials that would help patients guide when to hold it, so it's based on their own experiences.

DR. NARENDRAN: Thank you. Are there any other questions before -- Sabrina Numann? Ms. Numann?

MS. NUMANN: Sabrina Numann, patient representative. I do actually have a question that expands on that a little bit. This is based on my limited understanding of toxicity. I understand that they did some animal testing. I believe it was up to 10 times the human equivalent dose. But how would that equate to let's say a patient that was on the 3.2-milligram dose if they were to decide in an outpatient setting to take a pill sooner to mitigate some of their symptoms and they didn't feel that it was working?

It appears that the 4.0 milligrams was looked at the UK, so the 2.4 milligrams doubled, that didn't seem to be off too much by that, but

the 3.2 would be 6.4 milligrams if they were to decide to take 2 pills. So is there any information on toxicity in those levels and the human equivalent that that would be?

DR. WINCHELL: This is Dr. Winchell. Just to clarify, the medication comes in teenie-weenie little pills, so to get the 3.2-milligram dose, you're already taking 4 pills. So it's not just a matter of taking -- you would take a handful if you wanted to take twice as many. It does seem that patients can perceive that the medication is working, and they also can perceive when the medication is too much for them.

So we certainly saw instances in the clinical trial materials where the clinician wasn't able to take the blood pressure because a patient couldn't stand up, and patients would refuse medication because they felt dizzy, or they felt sedated. Could someone take too much? Yes, someone could take too much, and they would get syncope, hypotension, bradycardia. But this is a medication where people can seem to be able to tell

whether it's working.

If the sponsor's clinical folks want to expand on that, perhaps they could as well.

MS. GULLO: If it would be helpful to the panel, we do have a few cases where patients took more than prescribed, so we have some data on what did happen with those patients. It might also be helpful to ask Dr. Kosten to give his clinical perspective on what they see with clonidine, which is also prescribed as a tablet and has a similar side effect profile, which can help us -- he can expand from his patient experience in terms of how he advises those patients around dosing themselves.

DR. KOSTEN: The first thing is that I would certainly agree with the FDA in what's already been said. Patients are quite aware of when this is not working, which they still feel withdrawal symptoms and is the reason we are opting for the higher dosages. Once they start to feel withdrawal symptoms, they have a tendency to vote with their feet and walk away, and you have to get on top of these symptoms ahead of time. But on the other

side, if you took too much, you would in fact notice it by the first way, is you couldn't stand up. You get so much orthostatic hypotension that you just fall down, and that's going to be obvious to you but also the people around you.

We have had people who come into the emergency room with overdoses of clonidine, for example, and that has not just been an opioid withdrawal; it's been in people treated with hypertension also. Why? Sometimes because they're older and they made a mistake and took too many pills. Is it treatable? Yes, it's quite symptomatically treatable. It's not an acute emergency where someone will die from it or anything like that.

MS. GULLO: Also, just to clarify one of the earlier points by the FDA, we will absolutely take our best measures to educate physicians on proper patient selection and matching treatment setting to patient type. For patients that would be considered for home-based care, we would recommend that they have appropriate support systems at home

and caregiver support, not specifically for side effects of lofexidine but also because the withdrawal process is quite difficult to get through, and they are in intense distress through the process. So just to have a loved one, wife, daughter, son available is very important for the patients.

DR. NARENDRAN: Dr. Proschan?

DR. PROSCHAN: If we have time, I'd just like to expand on what I said at first about that plot. If we could see that forest plot that was shown. I think it was showing subgroups and completion status.

DR. NARENDRAN: Slide number? Is it sponsor's material?

DR. PROSCHAN: They showed it in response to a question.

DR. HERTZ: This is Dr. Hertz. We're referring to the applicant's slide on the demographics, the forest plot. Yes. Thank you.

DR. PROSCHAN: The reason I have a problem with that slide is it can only go to zero on the

left, which is -- from 1 to 0 is the most extreme possible change. On the other hand, on the right side, it can go all the way up. So when you see a confidence interval like this, it can be misleading because it looks like, oh, it's mostly favoring lofexidine, but that's because this plot really should be on a log scale, which would equate 2 with the half. In other words, an odds ratio of 2 in favor of lofexidine is really equivalent to a log ratio of a half. So those should be the same distance from 1, and they would be on a log scale.

So I think this is a misleading plot, but that's just -- I think it should be on a log scale.

DR. NARENDRAN: Thanks for pointing that out.

DR. HERTZ: This is more of a discussion and less of a clarification as just a general point. Let's hold that for later.

DR. PROSCHAN: Right. I wanted to raise that issue right after they showed it because they were responding to a question.

DR. HERTZ: Right.

DR. NARENDRAN: I think if there are no further questions, we could take a break for lunch. We'll reconvene in this room in one hour from now, 10 to 1. Please take any personal belongings you may want with you at this time. Panel members, please remember that there should be no discussion of the meeting topic during lunch amongst yourselves or with any member of the audience. Thank you.

(Whereupon, at 11:51 a.m., a lunch recess was taken.)

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

(12:30 p.m.)

Open Public Hearing

DR. NARENDRAN: We'll start. 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 is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance to the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to

address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

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

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

MS. PARRISH: Good afternoon. My name is Laura Parrish, and I am a parent. While I'm here

today to provide my perspective on today's conversation, I do want to share that US WorldMeds provided me with travel accommodations for me to attend this meeting.

My son Nicholas was addicted to pain pills. He became addicted in 2009-2010 during his senior year of high school. This addiction evolved into heroin use over the next several years. He died of a fentanyl overdose on April 11, 2016 at the age of 23. During this 6-year period of active addiction followed by periods of sobriety, Nick went through opioid withdrawal on several occasions, sometimes at home, sometimes while he was in treatment, and other times while he was incarcerated.

When these detox periods occurred at home, I was a witness to the withdrawal symptoms, horrible symptoms including nausea, vomiting, diarrhea, muscle cramps, loss of appetite, difficulty sleeping, periods of severe anxiety, and a racing heart beat. I've had the unfortunate experience of talking to parents of other people in addiction, and they had similar experiences when their

children detoxed.

In addition, I also volunteer at a men's recovery center and have so for the last three and a half years. I've had numerous conversations with the staff and many with those and people who are in recovery. While some still believe that withdrawal without medication is a reminder to the addict that they want to be, as they say, "don't want to be dope sick ever again," the tides are beginning to turn, and many feel that people are leaving detox because of the horrible withdrawal symptoms.

From the studies that I have been able to find online, the results related to lofexidine make it apparent to me that withdrawal symptoms alleviated by non-narcotic, non-addictive medication would only help these people remain in recovery longer. I believe strongly in the need for these medications to help alleviate these symptoms.

Nick and I often talked about the horrors of withdrawal. These symptoms kept him from seeking treatment on his own though he desperately wanted a

different life. I firmly believe the fear of withdrawal is what kept him from immediately seeking treatment at his last relapse. Even though he came to me and confessed that he had relapsed and was seeking medication-assisted treatment, he was not able to find a center before he passed away.

I also believe a medication such as lofexidine could potentially help curb what we now see as a current health crisis. Current statistics say that 4 out of every 5 heroin addicts began in their addiction with prescription pain pills. Patients should be properly assessed for dependency issues after being prescribed narcotic pain medication. If dependency is user noted, a medication like lofexidine could assist with the symptoms of withdrawal.

Shortly after Nick died, a co-worker came to me expressing his sympathy. He then went on to tell me he had had a minor surgery and had been given opioid pain medication following that procedure. He took the pain medication as

prescribed to stay ahead of the pain for two weeks. When he stopped taking the medication, he told me that he was sicker than he had ever been at any time in his life. He told me that he had never had a flu that made him feel as bad as he did after stopping the medication and that he desperately wanted to pick up the bottle and take more. Luckily this college professor had a sister who was a nurse and dealt in addiction. She told him he was going through withdrawal and that taking more would just prolong his withdrawal.

Over the years in my volunteer activities, I've heard many similar stories from those who had substance-use disorder. These people were not as fortunate and ended up going down a path that none of us could ever dream of going. Having a proper assessment and withdrawal medication regimen just might keep someone else from becoming addicted following a surgery or trauma that requires narcotic pain medication.

When Nick died, I committed myself to helping others in the hopes that no other parent

would have to go through what I've been through. The statistics at his death were that 129 Americans were dying every single day of a drug overdose. Last year, that number was up to 144, and the last statistic I saw was 177 per day. Drug overdose is now the leading cause of death in Americans under the age of 50.

This national health crisis requires us to seek different approaches to substance-use disorder treatment. Just as no one person comes into substance-use disorder along the same path, no two people can or will recover on exactly the same path. A medication such as lofexidine in the addiction recovery toolbox has the potential to put those in active addiction back on track toward a positive and productive life.

I encourage you to consider approval of lofexidine for the purpose of alleviating and easing opioid withdrawal symptoms.

DR. NARENDRAN: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any

organization you are representing, for the record.

DR. RIEDER: My name is Travis Rieder, and I'm a faculty member at Johns Hopkins in the Berman Institute of Bioethics, but I'm here representing myself. I have no conflicts of interest or funding to declare.

A few years ago, I was a junior faculty member at Johns Hopkins. I was working on issues very unrelated to what we're discussing today, mostly climate change ethics, and then I got hit by a van. I was on my motorcycle, and my foot was crushed. I was in a limb salvage situation they told me, and I would have several surgeries ahead of me if I were to keep my foot. The total number of surgeries ended up being six over the course of the rest of 2015, and I was in three different hospitals for the first five weeks.

The important point about all of that is that I was high on escalating doses of opioid medications for a long period of time. When I finally left the third hospital, I had undergone a free flap, which is a tissue transplant. It was a

9-hour surgery, and I was sent home on very high doses of oxycodone, extended-release oxycodone also known as OxyContin and the non-opioid gabapentin.

All I was told about these medications was to stay ahead of the pain, and so I did that. And at a two-month checkup, my initial trauma surgeon told me, "Oh, that's a lot of drugs. You really need to stop doing that now." So my prescribing physician, who was the plastic surgeon, gave me what I now know is a much too aggressive tapering regimen, according to which I would stop all of my medication in four weeks. I want to give you a sense of what withdrawal feels like from the inside.

During the first week, I told my wife, my mom, that I had what was the worst flu ever. I would get goosebumps while laying out in the August sun. I would shiver, and I didn't sleep very well. I was nauseated. I lost my appetite. But by about day 6, I started to recover a little bit, and I thought, "Oh, I can do this." I knew that I was in withdrawal, but I thought that I was getting

better, and I dropped my second dose.

The cruel joke of opioid withdrawal is that as you decrease the same drop each week. It increases the percentage that you're reducing, so the withdrawal during week 2 is much worse. All of the flu-like symptoms dialed up in intensity, and I started crying, which was strange, although I didn't know why. I made it through week 2, and I described it as miserable, the worst experience of my life but that's just because I didn't know what was coming.

During the third week of withdrawal, I was crushed by depression. The crying spells launched me into this very dark place where I became convinced that I would never be whole again. My body and my brain were irreparably broken, and what started to sneak up in the back of my mind was the thought that life isn't worth living if that's the way you feel. My partner was incredible, my wife. I had a 1-and-a-half year old daughter, and every day I stuck out another minute to try to become the husband and father that I used to be.

When I dropped the last dose and went 24 hours without any medication for the first time in months, I assumed I would die. I thought it was a genuine possibility that the withdrawal symptoms would kill me. I didn't know if that was possible. It turns out very unlikely. But if I didn't die directly from the symptoms, then I thought there was a real chance that I'd kill myself. I'd never been depressed. I'd never been suicidal. These were not demons that I had struggled with before, and I thought that the only way out was to go back on the pills.

So on day 6 of week 4, I finally gave up, and I told my wife to go refill my bottle of oxy. When she brought it back, I decided that I would try one more time to sleep. I hadn't slept in days. I hadn't slept at all in three days. I hadn't slept much at all in eight. She helped me upstairs, and I went to bed for the first time in weeks. And I put the bottle of oxy on the nightstand with a glass of water, and I told her, "If I'm still awake in 4 hours, I'm going to take a

pill, and we're going to deal with this again later." And 2 hours later, I was asleep. I slept for 6 hours that night, and when I woke up, the withdrawal symptoms had faded into the background. They certainly weren't gone, but I knew that I had made it out the other side.

I made it out. I was incredibly lucky, and I know that it was because I had a support system that not everybody has, and that I was just incredibly fortunate. As a bioethicist by profession, I have since moved all of my scholarly resources into the field of ethics of policy research around the opioid crisis. And one of the most obvious claims that no one is making that we should all be screaming from the mountain tops, I say humbly, is that for some reason we've decided the only way to decrease the prescription medication route into the opioid crisis is to cut the number of pain pills.

Now, there are problems with cutting the number of pain pills that most people in this room are probably familiar with, like there are people

in real pain, and opioids do help with some forms of pain like getting your foot blown open in a motorcycle accident. So the fact is we are going to continue using opioids until we have better medication for all forms of pain, and that means that cutting opioids is not an acceptable only alternative for avoiding the opioid crisis.

A really obvious second way is to make sure that those people who do get prescribed opioids have a way to get off of them, and withdrawal stands in the way of the most earnest, most desperate efforts. I don't know how I made it out of withdrawal without taking any more pills, but I am quite sure that if I had taken even one more, my path forward would have looked very different.

I am very grateful for your time for listening today. If you have questions about any of this, I have published and essay on this topic with some of the narrative in the Journal of Health Affairs, and I would be more than happy to address any questions and follow up if you wish. Thank you very much.

DR. NARENDRAN: Thank you. Will speaker number 3 step up to the podium and introduce yourself? Please state your name and organization.

MS. ELIAS: Hi. My name is Maureen Elias. I am an Army veteran with the Veterans Health Council of Vietnam Veterans of America. Thank you very much for allowing me to share my personal story about opioids with you.

If someone had told me that in 2016 I might become addicted to opioids, I would have laughed in their face. I didn't have time for any kind of drug use, unless you count the occasional glass of wine or chocolate bar. I was president of my university's study veteran association; vice president of the graduate student association; attending the Student Veterans of America Leadership Institute; taking a full load of graduate classes; and in case that wasn't enough, I was also a military spouse and a mother raising three children on the autism spectrum.

But everything came to a grinding halt when a 7-millimeter kidney stone lodged in my ureter,

blocking the flow from my kidney, and I was admitted for emergency surgery. Following this emergency surgery, I thought the pain would get better. I was very, very wrong. Within days after the surgery, I began to feel a lot of pain and pressure. I was told that this was normal with a stent, and I was prescribed three different forms of opioids: Opana, a long-lasting opioid, as well as hydrocodone and OxyContin, both short-acting opioids.

I remember sitting in the bathroom silently sobbing as I tried to go. The pain was excruciating, and the doses of opioid pain medication were increased to fairly high doses in order to allow me to function within my various roles. I was on these opioids for about a month when they finally took an x-ray and realized that my stent had slipped and was trying to exit from my urethra. No wonder I was in so much pain.

I had my second surgery within hours of that x-ray. As soon as the stent was removed, my pain was immediately eradicated. I went home that

day -- I remember, it was a Friday -- and immediately ceased all my opioid medications. Little was I prepared for the nightmare that weekend had in store for me.

Within 6 hours following the surgery, I began feeling very ill. I thought, "What kind of killer flu is this? I knew I would catch something going to the hospital." I was exhausted and constantly yawning, yet wide awake. My whole body ached. I was sweaty and yet freezing at the same time. My nose was runny. I felt like my heart was beating so fast it was going to burst out of my rib cage, and I began to run a fever; hence, my assumption that I had caught the flu. One particular symptom was that for some reason I kept feeling tears pouring from my eyes. As a veteran, I am not much of a crier, and this was very upsetting to my husband who never likes to see me cry.

Things got worse. My body was wracked with cramps from the nausea and diarrhea. In two days, I lost 12 pounds. Despite being buried under

mountains of blankets, I had goosebumps, and I felt so cold while simultaneously feeling like someone had set my body on fire. I thought, "I was dying." I considered taking more of my opioids thinking perhaps the pain had not in fact gone away. This might have become the beginning of an addiction to opioids because I was confusing the symptoms of withdrawal to the symptoms of my pain. Neither my ER doctor, nor my primary care doctor, nor any of the nurses that had seen me had mentioned anything about opioid withdrawal symptoms.

It just so happened that I was starting a chapter on opioids in my drug- and alcohol-use disorder class at school. As I read about the symptoms of opioid withdrawal, I knew this was exactly what I was suffering from. Relief poured through my body as I realized I was not in fact going to have to say goodbye to my husband and leave him alone to raise our three small children.

I read that by 72 hours, things were at their worst, and since I had just passed that time mark, I did not see my doctor since I knew the

symptoms would be decreasing shortly. Then I got angry. "How dare they," I thought. "How dare they not have prepared me for what I went through." Not even once were opioid withdrawal symptoms mentioned. Not even a cheesy cartoon flyer or a boring pamphlet was given to me. No preparations had been made to help me get access to medications that might have relieved my suffering and the toll on my already weakened physical state. Nothing.

I know I am extremely lucky because I was able to recognize that I had become physically dependent on opioids and was able to suffer through the withdrawal and have not had any signs of addiction since. But I was in graduate school and focused on drug and alcohol substance-use disorders. Not everyone has this type of serendipitous circumstance. Not everyone can discriminate between the symptoms of withdrawal and the symptoms of their pain.

While medical professionals can do more to prepare patients for the withdrawal symptoms of opioids, there is definitely a need in the medical

world for a non-narcotic, non-opioid medication to focus on withdrawal management for those wishing to discontinue use of opioids, especially for individuals like me who while not addicted have become physically dependent. In fact, I wonder how many patients go back on their opioid medications mistaking their withdrawal symptoms for the pain they were taking their medication for in the first place, therefore becoming accidentally addicted.

A medication like this could be a game changer in preventing accidental addictions. Thank you for your time.

DR. NARENDRAN: Thank you. Will speaker number 4 step up to the podium and introduce yourself? Please remember to state your name and organization you may be representing.

DR. WOLFE: I'm Sid Wolfe, and this is prepared in conjunction with Dr. Foster, who is a neurologist and is doing a preventative medicine residency at Johns Hopkins, and we are fortunate enough to have him working with us for a couple months. We have no financial conflicts of

interest.

The first slide is really the way Dr. Hertz described some of these dichotomies, is what's the relationship between mitigation of withdrawal symptoms and facilitation of completion of detoxification, and whether the data support both claims. If completion of detoxification is some moderately long-run, not too long and not too short, interval by which you say, aha, it's now a month or whatever afterwards; is there a difference between the placebo in the other group? That would be one thing.

Is it possible to make a claim of symptomatic relief without longer term evidence that the effect translates into detoxification? Well, the proposal by the company and the studies are really looking at the symptomatic relief and really not much more than that.

(Pause.)

Let me just read what's there, if we can't get to the next slide.

So part of the answer to the question is,

the withdrawal is the first part -- everyone in the room knows that -- but it's a means to an end. And without really measuring the extent to which the end is met, we just don't know that. So the purpose of this first part is to enable people to really treat the larger problem.

The third slide is the exact labeling, which has been in effect for about 25 years of Britannia's version of lofexidine. "Initial doses should be 0.8 milligrams per day and divided doses may be increased up to a maximum gradually of 2.4 per day. Maximum single dose should not exceed 0.8 milligrams." Then it goes on to say that where there isn't any opioid use during the detoxification, duration of treatment should be 7 to 10 days. And then at the end, they recommend tapering off of lofexidine and another additional period of 2 to 4 days.

Thus, the approved -- and it's been the case for a long time -- starting dose is 0.8, one-quarter of the U.S. proposed 3.2-milligram by World Medical. Maximum dose is 2.4, which is

two-thirds of the U.S. proposed dose. And the duration of treatment is from 9 to 14 days with gradual dosage reduction.

I'll read the next slide. "Discuss the adequacy of the available safety data to support use between 7 and 14 days. Treatment during the submitted trials last 5 to 7 days. Only 37 subjects were exposed to 2.4 milligrams for more than 7 days only; 14 subjects were exposed to any of the lofexidine dose for more than 14 days." Lacking data, one can hardly support the adequacy of use between 7 and 14 days. This is especially a problem for people that are taking extended-release doses as opposed to immediate release because they will have a longer period of washout.

This is just on the benefit harm ratio. In the upper right, this is looking at the 5-day completeness, the completers, 47 percent with the 3.2; 46 percent with the 2.4. At 8 days, those numbers were 41 and 40. There was no difference on that measurement of completers, and as you saw, there's no statistically significant difference in

symptom improvement with either of the doses. On the other hand at the bottom left of the slide -- this is the same data the FDA presented this morning -- there are serious treatment emergent adverse events: syncope, hypotension, and bradycardia. 3.2 and 2.3 percent total of the people were zero at 2.4 dose. So the benefit is no greater and the risk is higher.

I'll just skip to the last question. Do you recommend approval? No, for the following multiple reasons. Given that there's only one randomized control trial for 2.4, how can the advisory committee recommend or FDA approve the 3.2-milligram dose that is no more effective in trial completion but is significantly more dangerous than the 2.4 dose?

Unless the advisory committee and the FDA believe that for the past 25 years, the UK has erred in approving lofexidine, why is the proposed U.S. starting dose 4 times higher than that in the UK -- 0.8 as opposed to 3.2 -- the daily dose 50 percent higher and the recommended duration 9 to

14 days instead of 5 days?

Why, especially given the previous opioid use history of those in these trials and of so many others, are companies not required to have much more adequate patient follow-up before raising their currently misleading victory flag?

I would just say in closing that even if there were the right dose of some medicine like this, we haven't gotten there yet. To have a pretty much flat line in terms of benefit between 3.2 and 2.4 means we probably could go to an even lower dose of this or some other drug, and thereby, by definition, reduce the risk. The risk is going down even between 3.2 and 2.4, and it would go down farther. So I think for this advisory committee to recommend approval of this drug is to recommend a drug that is at clearly too high a dose. Thank you.

DR. NARENDRAN: Thank you. Will speaker number 5 step up to the podium and introduce yourself? Please state your name and any organization you may be affiliated with.

DR. POLANIN: Thank you for the opportunity to speak today. My name is Dr. Megan Polanin. I'm a senior fellow at the National Center for Health Research. Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from the drug or medical device industry, and I have no conflicts of interest.

Opioid withdrawal symptoms affect functioning and quality of life for both patients with OUD and those who take opioids appropriately. Withdrawal symptoms deter patients with OUD from seeking treatment and contribute to their continued use of opioids. We can all agree that there is an unmet need for non-opioid alternatives. FDA scientists stated that these alternatives must show substantial evidence of effectiveness and that they facilitate completion of opioid withdrawal management.

If approved for both of the proposed indications, lofexidine would be the first

non-opioid approved for treating opioid withdrawal and the only product approved to support completion of opioid discontinuation treatment. This drug would set a standard for future drugs to meet. Thus, it is important for this committee and the FDA to make decisions based on sound science and strong data.

We have concerns about the efficacy and safety of this drug. The data provided offer limited information about lofexidine's efficacy. For study 3002, treatment time was 5 days and only half of patients who took the drug completed the treatment period. In the 3001 study, treatment time was 7 days and only 41 percent of patients who took the drug completed this treatment period. Generally speaking, patients who took lofexidine reported lower severity of opioid withdrawal symptoms and completed treatment at higher rates compared with placebo groups for up to 7 days.

What are the implications for the real world? Treatment took place in controlled inpatient settings, so we don't know how well this

drug works in other settings. Benefits were demonstrated only in patients discontinuing opioids abruptly, so we cannot assume that this drug works for gradual opioid tapering, which is a common practice. Finally, we don't yet know whether lofexidine will continue to help reduce withdrawal symptoms or discontinue opioid treatment after one week.

Lofexidine use is associated with cardiac related safety issues. The sponsor's current data, as well as data from the UK, show that there are cardiac related safety issues particularly at the higher 32-milligram dose. They included low blood pressure, orthostatic hypotension, syncope, and bradycardia. Females taking lofexidine were at higher risk of developing hypotension and bradycardia and were twice as likely to experience syncope.

These cardiac events could have implications for severe cardiac events in the real world. In the current studies, these events were bothersome enough to make patients quit taking lofexidine. In

many cases, cardiac events were sufficiently severe for doctors to stop administering the drug. Keep in mind that individuals who had cardiac issues such as uncontrolled arrhythmia, high blood pressure, low heart rate, and symptomatic bradycardia were excluded from at least study 3002. Thus, we do not know how this drug would affect patients with existing cardiac problems.

Today the committee must decide whether the current data support lofexidine's efficacy and whether the benefits of this drug outweigh its risks, and if so, for whom? Data show that this drug can provide symptomatic relief of opioid withdrawal symptoms for up to 7 days. Reducing opioid withdrawal symptoms for this long may be sufficient to help people get off of opioids temporarily, however, this is only one element of addiction management. What is most important is helping individuals stop taking opioids completely.

The sponsor's proposed second indication is that lofexidine facilitates completion of opioid discontinuation treatment, however, they have

provided no long-term data to support that indication. Ideally, this drug should be used as part of long-term treatment for managing opioid-use disorder after a patient stops taking opioids. We respectfully urge you to let the FDA know that they should require evidence that this drug helps patients complete opioid discontinuation treatment rather than approving this indication based on the current data.

In summary, patients undergoing opioid withdrawal need non-opioid effective treatment alternatives. In order to ensure that we are doing more good than harm, the FDA must ensure that treatment show substantial evidence of effectiveness. Current data indicate that lofexidine can successfully provide short-term relief to patients' opioid withdrawal symptoms following abrupt discontinuation of opioids. However, due to cardiac safety risks, this drug should not be indicated for individuals with existing cardiac conditions, and if approved, there should be a clear warning on the drug's label.

Finally, the sponsor has not provided sufficient evidence that lofexidine increases the likelihood that individuals will complete withdrawal treatment and end their physical dependence on opioids. We believe they must do so in order to receive this indication. Thank you for the opportunity to share our perspective.

DR. NARENDRAN: Thank you. Will speaker number 6 step up to the podium and introduce yourself? Please state your name and organization you are representing.

MR. BIELECKI: Good afternoon. My name is Pat Bielecki. I would like to thank the Food and Drug Administration for allowing me to speak here. I also would like to thank US WorldMeds, who provided my travel from Phoenix and my lodging.

In 1994, the Phoenix fire department lost their first firefighter to opiates. It was the same year that I injured my back. Since 1994, 16 firefighters from Phoenix have died from an overdose from opiates or suicide. Fifteen of those deaths were attributed to opiates. So in 1994, I

started my long battle, what I call unintentional addiction. You get hurt, you get on it, and you can't get off it. You're afraid to tell anybody.

I must have tried at least 20 or 30 times over my 15 years dealing with this. You deal with the pain. You deal with the opiates and the rejection. First starts the panic when you're coming off it or getting low on your pills. That hasn't been mentioned yet. That's overwhelming. I would have done anything to get the pills. I was fire chief on the job, but I would have still probably took them from somebody if I needed to.

After 5 to 15 hours without the drug, you start experience flu-like symptoms. That's been mentioned; nausea, cramping, depression, muscle cramps, diarrhea. Worst of all for me was the lack of sleep and the tingling in the lower extremities. The literature states that within 72 hours, the symptoms peak. Don't count on that. Length of time on the drug and what the dose is determine that for you. It would take me a good month or so to get my sealegs back where I felt totally

comfortable at work or wherever I was.

You can't work. You can't sleep. You can't play with your children. You can't do anything. You can't keep a relationship pliable if you're trying to withdraw off these medications. Your life is on a standstill for the first month or so.

For most of the years I was addicted, I told no one. It was a secret. My wife didn't know about it. I felt if somebody knew what I was doing, I would be weak and my job would be in jeopardy. And what would my wife and family think? It was the big secret. I kept it for 15 years. Nobody knew I was taking the medication; multiple doctor visits, stealing some pills from family members. I did everything where I could stay pliable within the organization.

If the medication that you are here to review can reduce the physical effects of opiates, I wonder how many of those 15 firefighters who died from opiate addiction over the last 20 years, would they still be here? They did not want their secrets out, so five of them took their own lives.

I have been sober for over six years now. I used suboxone to get off the pills. The problem with suboxone or methadone, you're trading one addiction for another. I would like to thank everybody for allowing me to speak, and have a great afternoon.

DR. NARENDRAN: The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as public comments. We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Dr. Sharon Hertz will provide us with a charge to the committee.

Charge to the Committee – Sharon Hertz

DR. HERTZ: Thank you.

There is a lot of misunderstanding of the data surrounding the management of opioid-use disorder. As described in several presentations today, there are data that show long-term success for individuals is much greater when it's accompanied by long-term treatment using some form of medication-assisted treatment such as methadone, buprenorphine, naltrexone, along with psychosocial treatment. This is more successful than psychosocial treatment without subsequent use of MAT -- the long-term treatment is much more successful when it's done in conjunction with MAT than without. Least successful in terms of long-term management of opioid-use disorder is the use of psychosocial treatment alone.

Withdrawal management, which is what we're referring to the function of lofexidine here, without the use of MAT is associated with higher rates of relapse to illicit opioid use compared to maintenance treatment options, and because patients who have been detoxed are no longer physically opioid dependent or tolerant, the relapse places

such patients at greater risk for death due to overdose.

During this meeting, you've heard data from the clinical trials performed to support the safety and efficacy of lofexidine in assisting withdrawal management during abrupt discontinuation of opioids. The company is interested in exploring two indications, the first being the reduction of symptoms of opioid withdrawal in the context of abrupt discontinuation and increasing the likelihood that withdrawal treatment will be completed.

I just want to make sure that we're all speaking the same thing, and for the record, that withdrawal treatment is not the same thing as long-term management. It is simply the process whereby one comes off the opioid following an abrupt discontinuation or detox. We're not talking about long-term medication, long-term management, or maintenance of sobriety.

In clinical circumstances where abrupt rather than gradual discontinuation of opioids may

be preferred, withdrawal symptoms can result in failure to complete the withdrawal process, placing people at risk for relapse. With the completion of withdrawal as the goal, we ask you to discuss the relationship between mitigation of symptoms of opioid withdrawal and facilitation of completion of detoxification.

Can the clinical significance of a reduction in opioid withdrawal symptoms be determined based on achieving statistical significance alone or is the ability to remain opioid free until withdrawal is complete data necessary to determine the clinical meaningfulness? In other words, if patients have some relief of symptoms but are still too uncomfortable to complete the withdrawal process, is there any clinical relevance of a statistically significant difference in withdrawal symptoms across treatment groups?

The clinical data submitted in support of this application reflect the lofexidine dose of 3.2 milligrams a day, approximately twice that described in the literature. Only one study

provides data to support a dose lower than 3.2, but we've described some additional data that may explore or support other dosing regimens. The data also indicate dose-limiting adverse events, including hypotension, bradycardia, and syncope. We ask for your thoughts on what dosing regimen should be recommended.

There are no data supporting the use of lofexidine in the common scenario of gradual opioid taper and for use beyond 5 days, which, as we've heard during the open public hearing, could be useful in the context of situations of tapering opioids after chronic analgesic use.

The lack of evidence of benefit for longer term use is of particular concern given the observation that lofexidine may have effects on cardiac induction, perhaps not clinically significant when used alone, but more so when in conjunction with other drugs that are QT prolongers. Are these gaps of information concerning the longer term safety and the longer term efficacy something that should be addressed by

the applicant, and if so, are they appropriate for postmarketing studies?

So these are the overall types of things we're going to ask you to discuss and ultimately vote on. Your deliberations and recommendations, as always, play a very important role in our decision-making process, and I'd like to take this opportunity again to thank all of you for taking time from your extremely busy schedules to participate in this meeting.

Questions to the Committee and Discussion

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

Question number 1 is a discussion question. I'll read the question.

Two concepts are under consideration, mitigation of symptoms associated with opioid

withdrawal and facilitation of completion of abrupt opioid discontinuation treatment in patients with opioid-use disorders. Discuss whether an effect on completion rates of abrupt discontinuation treatment is necessary to establish the clinical relevance of the efficacy data for mitigation of symptoms associated with opioid withdrawal. Could a finding of efficacy be made without data supporting both?

Whoever is ready to discuss could just start, and then we'll make sure that everybody has an opportunity to say something at the end. Dr. Turner?

DR. TURNER: Yes. I guess I'm wondering from a regulatory standpoint how common it is to require a measure of statistical superiority over the comparator versus clinical relevance, because I can think of many indications where drugs are merely statistically superior. Antidepressants come to mind, where a typical trial is up to 8 weeks; meanwhile, in the real world, people take them often for many years. The data in the

clinical trial programs often don't speak to what actually happens in the real world.

I don't know if that makes sense. In other words, is this common to stipulate that we need clinical relevance in addition to a finding of statistical superiority and that there is some mitigation of symptoms?

DR. HERTZ: This is Sharon Hertz. I'll speak for my division, which has several therapeutic areas, and this certainly holds true for many of our products. It's possible to have a statistically significant difference that is small and really cannot be expected to have any clinical relevance, so we often ask for some additional data to support why that difference is sufficient, clinically relevantly sufficient, to support an actual approval for the proposed indication.

Conceptually, one could simply overpower a study to improve the chance of a statistically significant difference. That's not meaningful. Here, I don't think the studies have an appearance of being overly powered -- they weren't very large

studies -- but given that this is a relatively new therapeutic approach or a drug for this particular indication, we don't have an established set of data that show the association between just a difference in the scores for withdrawal and ultimate success for completing opioid withdrawal or detoxification in an abrupt way.

In clinical settings where those relationships already exist, it may be sufficient to just provide a certain amount of information. But as you've heard, this is relatively new and not widely explored in our experience, which is why we're very interested in trying to establish clinical significance for the difference in symptoms rates.

DR. TURNER: If I could just follow up and give an example from some other -- I'm not a cardiologist; I'm a psychiatrist, but I'm thinking of statins. And I believe statins, there's no question they can do a big number on lowering one's total cholesterol, but if one looks instead at the decrease in heart attacks and strokes, then it

becomes very iffy as to the clinical relevance, which many people would argue that is more clinically relevant. But I don't believe that was held up as a stumbling block for the approval of those drugs.

DR. HERTZ: Well, in fact, that's not quite correct. There are well known associations between certain outcome measures and long-term cardiovascular endpoints so that shorter term endpoints can be used as surrogates for long-term health. So for instance, we know that ultimately on a population level, if you lower blood pressure, you're going to have better outcomes. The same is true for lowering lipid levels. That has been established over time. So now the reliance on certain outcomes like lipid levels is appropriate.

Now, I don't know the specifics of how they do it because I don't do that in our division. But yes, we believe that there is an association long term between managing lipids and cardiovascular outcomes.

The difference here is quite important. We

are not talking about the long-term outcome of opioid abstinence. That's something that we are interested in when or -- not even abstinence, but management of opioid-use disorder. So we've had advisory committees where we've talked about our approach for finding products to treat opioid-use disorder, and that is not what we're doing here.

What we're doing here is a very specific, limited activity or event. This drug, the company is requesting -- the applicant is requesting that this drug be approved for the purpose of ameliorating the symptoms of opioid withdrawal, and they also are interested in demonstrating its effect on completing withdrawal from opioids abruptly.

There is no claim that this is going to have a benefit for long-term treatment of opioid-use disorder, and we're not asking you to consider that. But within the context of the two elements of what the applicant is asking, we want to understand if you feel that relationship is important, and if so, to discuss that further, both

the reduction of symptoms and completing the withdrawal from opioid activity.

DR. NARENDRAN: Dr. Proschan?

DR. PROSCHAN: Yes. I'm Mike Proschan from NIAID. I believe that it's important, the completion is important, in part because it helps convince me that what you're seeing is real because I worry about missing data clouding the issue, and the fact that more people are completing under drug than under placebo has a big effect on me in terms of whether I think it should be approved. So for no other reason than that, I would say it is very important to show a benefit on rates of completion.

DR. NARENDRAN: Dr. Dunn?

DR. DUNN: Hi. Walter Dunn. I wanted to follow up on that question about what constitutes completion of abrupt opioid discontinuation. In these two studies, we have day 5 and day 7 data. I'm wondering clinically and if the FDA agreed with these endpoints. Certainly, they reached these endpoints based off of the prespecified criteria, but clinically how relevant is that, where the

opioid discontinuation withdrawal stops at day 5/day 7? Once you reach that point, are you home free?

It sounds like there's a lot of heterogeneity in terms of not only the symptoms that you're exhibiting but the potential time course of that withdrawal process, so I'm just wondering how relevant is this day 5/day 7 endpoint.

DR. HERTZ: This is Sharon Hertz. I'm going to answer your question with a question. I'm trying to understand if the goal is to attempt to withdraw somebody from an opioid over 5 or 7 days, and that is the sole goal, not long-term management or maintenance of anything, why would you question if that's relevant and in what way would you like to see that additional information or something different about that?

DR. DUNN: This not being my area of expertise interest of addiction, I would have proposed perhaps looking at the withdrawal scales to see if they reached a score of 0 or 1, something

minimal in terms of the degree of discomfort the patient was feeling. So instead of prespecifying a specific limited time course, looking at how long it takes or the number of patients that reach a score of zero. And I understand that perhaps in study design, that would be extremely difficult given the heterogeneity of the withdrawal time course, but I would have looked at some of the COWS and SOWS scores to see what percent of patients were able to reach that zero score.

DR. HERTZ: So you're saying that in addition to comparing the symptoms over some period of time and in addition -- maybe I should say are you saying that in addition to looking at the symptoms over time and in addition to measuring the relative rates of successfully taking somebody off the opioid, in addition to provide clinical context or relevance, you would like to see what the actual withdrawal symptoms are at that point?

DR. DUNN: At that point and also perhaps the number of patients who are able to reach that score such that their potential risk of relapse is

mitigated.

DR. WINCHELL: This is Celia Winchell. When these studies were designed, I remember there being some assumptions made about we think we know the peak is going to be on day 2, but if it isn't on day 2; and we think that withdrawal will take 5 days, but if it takes more? And a lot of what we saw in the data actually was somewhat reassuring. You could see that by the end of the observation period, the placebo and active groups were really converging, maybe because the placebo people who were uncomfortable left, but mostly everybody who was still left was pretty comfortable. So that was reassuring, but I agree that we can look at the final score that people had before they walked out the door, whether that was the protocol specified period of observation or some time before.

One of the things Dr. Horn observed in her analysis was that it seemed like there were people who felt fine and didn't want to stick around anymore. Whereas we often impute non-response to non-completers, in this case, it didn't necessarily

seem to be that people were leaving because they were non-responders; they'd gotten what they needed it. But we'll take a closer look at that.

DR. NARENDRAN: Dr. Jain?

DR. JAIN: This is Felipe Jain. Regarding these two concepts under consideration, to me both are important and one does not necessarily imply the other, but both could be important in reducing the stigma that prevents some patients from seeking detox from opiates.

As we heard from both members of the audience, as well as I think what the broader literature suggests, many people do not seek treatment because they're afraid of the withdrawal symptoms. So if the drug demonstrates efficacy for the symptoms, for statistically reducing the symptoms of opioid withdrawal, I believe that a label that includes that information might have public health relevance.

I think the other question is obviously also of great importance of whether a completion of the abruptive opioid discontinuation treatment occurs,

and I think that's a stronger measure as it's a behavioral measure. But I wouldn't want to minimize I think the potential importance of describing the drug in the various ways in which it may work and may be helpful to the patient who's taking it.

DR. NARENDRAN: Dr. Carroll?

DR. CARROLL: I want to echo that point. Having worked with these patients for a long time, detoxification is an enormously difficult process, and the small differences can feel pretty big to the patients. But I've been curious -- and I'm glad that Dr. Dunn brought it up -- about how one is defining completion of detox because 5 to 7 days is extremely arbitrary with a phenomenon that has so much interindividual variation.

With your point about this being a relatively new area for the FDA, I strongly think it makes sense to actually look at when patients get to the lack of discomfort because it's a very variable kind of point, and that's really the completion of the detox for that particular

patient, not the 5 day thing. So I think there would be some value to looking at that data on a more individual basis and who gets to zero on the SOWS or the COWs.

DR. NARENDRAN: Ms. Witczak?

MS. WITCZAK: Yes. Kim Witczak. I guess on the two concepts being discussed, the mitigation of symptoms, I think that's an important -- I mean, obviously, clearly you heard it from the audience. But I think when you start looking at that complete abrupt -- the discontinuation facilitating it and looking at 5 to 7 days, hearing what the UK does, I think that's a really missed piece of information here today that I would have loved to have seen a presentation and really would want to know why they had recommended a longer length of time.

So I feel like there are two different things, and I don't think that you can say one is going to automatically mean the second because I know in the world of advertising and when it gets into the real world and how it gets promoted, there's a lot of potential. People are desperate.

But I think abrupt -- and then hearing that gentleman in the audience earlier talk about the gradual, I wonder once it's, again, into the real world with the GPs and people, will there be a distinction between abrupt and withdrawal or abrupt and the gradual withdrawals. So just some things to look at.

DR. NARENDRAN: Dr. Pickar?

DR. PICKAR: Yes. Dr. Hertz, I agree with this discussion going on right now, and if you treated people with opioid addiction as I have, it is a tough, tough thing. I appreciate your point, Dr. Hertz, that you're focused on these two questions in an FDA regulatory fashion, but there's not necessarily longer term outcome. I'm just saying that's a different question.

On the other hand, is there anybody here who doesn't think that if you get through 5 days, that is implication for longer term? If there was no association between a 5-day success and long term, we wouldn't be having this conversation. So I think that's an unfair position you're taking just

focusing on this. This is built into this. If 5 days withdrawal had no implications for successful -- I happen to think it does, but if it had none, then there would be no conversation. So I think your overly focus just on those two questions is off the mark.

Now, I'm so sorry that we didn't have 1-month, 2-month follow-up on these patients. That would have been so easy to do, and it would have been profoundly important not just for ruling on this particular drug, but for a treatment, which I may add, Dr. Hertz, has been available to the public for over 30 years. The first use of alpha-2 agonist was when I was a resident, and it was done in the hallway down from where I was a chief resident.

So this has been around for a long time, and there is an implicit thing here. It would have been in my mind that if you get through detox in 5 days, it has bigger implications. So I'm with you, Doc, but it's hard for me just to narrow it down to these two questions because implicit in the whole

thing is that this has broader implications. Just a thought on a tough question.

DR. NARENDRAN: Dr. Jeffrey?

DR. JEFFREY: Yes. Hi there. Jessica Jeffrey. I just want to echo Dr. Carroll and Dr. Jain. [Indiscernible - audio gaps]. It takes multiple times for patients to successfully complete discontinuation. [Indiscernible] -- and I think we can't minimize the importance of making our patients comfortable. I think both of these issues are important, but we can't [indiscernible.]

DR. NARENDRAN: Thank you. Dr. Fiedorowicz?

DR. FIEDORORWICZ: It's a nice transition for my comments. I agree with what people have been saying before about the need to individualize their assessment and what constitutes completeness for an individual patient, and that 5 days may be arbitrary, and we are all interested in long-term outcomes as much as this discussion has focused on. But I agree with Dr. Pickar that that's in some ways a different question here.

While we don't know whether the outcome of

this study is a relevant surrogate for a long-term outcome, we are called upon at this time to discuss the clinical relevance of this efficacy data. And those of us who care for those who are suffering are dealing with opioid withdrawal, and from what we've heard in the testimony today from family members and those individuals afflicted with that, there is tremendous human suffering associated with withdrawal, and it seems to me that the alleviation of that suffering is certainly clinically relevant in and of itself in an ipso facto way.

I'm going to save discussion about the second indication because I think we have that as for item 3 on the discussion because I think there are several relevant points there that have been coming up. Thank you.

DR. NARENDRAN: I want to agree in terms of I feel psychiatry drugs or addiction drugs are held to a different kind of standard than medical drugs. I feel like it is pretty well established that if you can get them to be comfortable and it reduces symptoms, that is very clinically meaningful. I

think the 5 day/7 day, it's nice that they were able to show that, but I wouldn't think that that absolutely has to go hand in hand because it is only relevant to the extent of how it was done.

Again, these are people who are inpatients, and if these people had easy access to heroin in their homes and they had done it, would it really have made the difference? Probably; probably not. We don't know that. So I think in terms of the fact that it reduced their discomfort, we have evidence for that, and rater-observed evidence signs, that in itself should be sufficient for a narrow indication I think.

DR. WINCHELL: Could I just make one comment? This is Celia Winchell. Let me just clarify why we're asking the question. We have two studies that used symptomatic assessment, a patient-reported outcome. They show a statistically significant difference, yes, in fact, quite an impressively significant difference. For example, one of them shows a difference of 0.2 units on a scale that goes up to 30.

What we're asking is if we had that by itself, would you be convinced or do you think that the completion rate serves as almost the bioassay of the relevance of this mathematical observation?

DR. NARENDRAN: I would not be convinced if it was 0.2, but I feel the completion rate in conjunction with this strengthens the data for sure, and from a regulatory standpoint, that probably makes more sense. If they do and can show a functional outcome, it's strong, but you also have to take into account the pathophysiology and the process of what we're studying to see if that makes sense.

Dr. Fiedorowicz?

DR. FIEDOROWICZ? Yes. Can we clarify? I don't recall seeing one where the difference in the units of the scale was 0.2. I recall it being over 2. So I think if we're staying within the units of the scale, I think that's important to clarify.

It's also maybe worth mentioning a reference that was highlighted in the materials, and this was a paper by Margaret Vernon on addictive behaviors,

2016. It did not look as far as outcomes, as far as what difference on the scale makes for people actually completing treatment, but it did look at scores with this compared to modified clinical global impression severity ratings to try to get a sense of what threshold might be clinically relevant. And that article suggested that a difference of 2 to 4 units on this scale might constitute a clinically meaningful difference.

DR. NARENDRAN: Dr. Proschan?

DR. PROSCHAN: I think what she's talking about is slide 31 of the FDA presentation, the SOWS for days 1 through 7, which showed a difference, the 2.4 dose versus placebo is a difference of 0.2 and the 3.2 dose shows a difference of 0.3 relative to placebo.

DR. FIEDOROWICZ: Is that in units of the scale?

DR. HORN: Dr. Petullo?

MR. PETULLO: I believe that's log transformed data, correct? Our next slide shows it in its day 5. One more slide. That's transformed

data.

DR. NARENDRAN: Should I summarize or did you want the sponsor to have an opportunity to -- Dr. Hertz? The sponsor can comment.

MS. GULLO: Thank you. First, I'll just clarify that the data that was on that last slide was log transformed data. You saw in the SOWS and COWS both the curves that we showed, but more specifically the SOW, that the difference that we saw, especially during peak days of withdrawal, were ranging between 2 and 4 points like the paper that was just referenced.

Also, based on the discussion that just occurred, we thought it could possibly be helpful to clarify that we did collect 30-day follow-up information on patients. Of course this was exploratory. It's primarily for safety, but we did also assess current treatment status in these patients. The protocol required that we would follow up with patients attempting at least 3 times. We were successful in contacting 57 percent of patients in study 3001, and because we would not

expect there to be a treatment effect at this point, we did look at outcomes based on whether they completed the prespecified 7-day protocol. So I can go through that data with you.

Slide 2 up, please. As I mentioned, we collected the data in 57 percent of participants whom we were able to reach. We did contact 57 percent of patients. We evaluated their current treatment status based on whether they had or had not completed the 7-day period. And in those that had, using that number as the denominator, 75 percent of the patients that completed were reporting having either been engaged in subsequent treatment or reporting abstinence compared to only 30 percent of the patients that we knew did not complete the study.

Again -- and I don't think we can emphasize this enough in agreement with the agency -- we do not consider lofexidine as an addiction treatment. It is a treatment for opioid withdrawal. But based on the discussion of 5 or 7 days and is that arbitrary, the scale data do clearly show that most

symptoms had resolved about that time, and this data I think supports the importance of getting through that critical period to create any opportunity for continuation of care for these patients.

DR. NARENDRAN: Thank you. I feel like we heard a range of opinions, but there were some people who felt the symptoms reduction in itself is clinically meaningful and valuable to have in treating patients like this. There seemed to be a lot of people who agree with that. Some of the folks clearly felt it is good to have a clinically relevant completion rate endpoint, and the best of both worlds would be to have both.

Does that summarize the discussion? We could move to question 2, which is a voting question. Do the data provide substantial evidence of effectiveness of lofexidine for the mitigation of symptoms associated with opioid withdrawal?

Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the

button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

Go ahead and vote.

MS. WITCZAK: Can I ask one question? It says with opioid withdrawal. Could it be revised to say "abrupt"?

DR. NARENDRAN: The question could be revised to say "abrupt" opioid withdrawal?

DR. HORN: Yes, you should consider it abrupt.

(Voting.)

MS. BHATT: We are waiting for Dr. Jeffrey to vote, so we're processing everything.

The voting results yes, 12; no, zero; abstain is zero.

DR. NARENDRAN: The third question is a discussion question. Discuss the appropriateness of including facilitation of completion of abrupt opioid discontinuation treatment as a second

indication. Is this supported by the data provided?

I guess everybody has an opportunity to say why they voted yes. I got a little overzealous and moved through. So we'll have an opportunity to go around the room and make a statement as to why you voted yes. We'll start from that side of the room, Dr. Carroll.

DR. CARROLL: Within this fairly narrow indication and for the data provided, it's clearly better to be on lofexidine than not on lofexidine. The effect size is small, but it's there, and anything that we can do to help, even modest, makes sense.

DR. BRADY: I really don't have anything to add. I think the data speaks for itself within this limited indication.

DR. PROSCHAN: I'm Mike Proschan, NIAID. I think the FDA analyses are consistent with the sponsor's analysis. I think there's no question that they've shown efficacy, and I think both sides agree with that.

MS. NUMANN: Sabrina Numann. I did vote yes. I feel that the evidence was definitely there to support that. Thank you.

MS. WITCZAK: Kim Witczak. I voted yes with the addition of putting the abrupt. Still narrow small numbers, but I think the numbers justified it.

DR. PICKAR: I voted yes. I think the data's there.

DR. TURNER: This is Erick Turner. I voted yes also. I thought the analyses were -- everything was highly significant, but p-values can be misleading, so I calculated standardized being differences that came out 0.3, which is like antidepressants, which are nothing to write home about, to 0.5, which are better than antipsychotics in that range. And equally important, it was robust to the various sensitivity analyses. If it had been marginal, I'm sure we would have seen some non-significant results somewhere.

DR. NARENDRAN: Dr. Jeffrey?

DR. JEFFREY: Hi. Dr. Jeffrey here. I voted [indiscernible - audio gap].

DR. NARENDRAN: Dr. Narendran. I voted yes just based on the data, which seemed to be strongly supported.

DR. JAIN: Dr. Jain. This is an extraordinarily difficult cluster of symptoms to treat, and I felt that the differences shown were clinically meaningful.

DR. DUNN: Walter Dunn. I voted yes. I thought the scales that they used were an appropriate assessment of the patient's symptoms and discomfort, and it appears that the score differences were in the clinically meaningful range.

DR. FIEDOROWICZ: This is Jess Fiedorowicz. For the reasons stated, I thought the outcome was clinically relevant. The observed effects were small but not negligible and supported by two pivotal trials across both industry and FDA analyses and across both primary and secondary outcomes.

DR. NARENDRAN: Thank you. Now we can move to question number 3. It's a discussion question. Discuss the appropriateness of including facilitation of completion of abrupt opioid discontinuation treatment as a second indication. Is this supported by the data provided?

Who wants to go first? Dr. Fiedorowicz?

DR. FIEDOROWICZ: I think there are two pieces to this that we need to talk about. The first piece relates to the FDA presentation that mentioned that this indication is not a specific disease or condition and the recommendation that this could be included in the clinical studies section. If that is indeed what we feel, then we may not need to have much further discussion.

However, the second piece is do we feel that the studies were designed to support this and is there enough long-term data in these studies to support the indication? My comment was mainly to frame it, that I think there are two pieces we need to grapple with, is this a reasonable indication to seek, and then the second is, were the studies

designed to support this indication.

DR. NARENDRAN: Who wants to go first? Dr. Proschan?

DR. PROSCHAN: I'm sorry. The tail end of that last question, I actually also did a calculation of what the difference is, and I get more like 1 and a half to 2 points rather than 0.3 to 5 based on that log change. I just wanted to say that.

DR. TURNER: It's a different calculation, standardized being difference. You divide it by the standard deviation, you get units. The units are numbers of standard deviation, separation between drug and the comparator.

DR. PROSCHAN: I thought you were talking about the numbers [inaudible - off mic].

DR. TURNER: No.

DR. NARENDRAN: Ms. Numann?

MS. NUMANN: I was wondering if you could help clarify for me what you mean as second indication and to clarify if the FDA does indeed consider that.

DR. WINCHELL: Let me just start. These two different claims about the effect of a medication are proposed to be included as indications, in the indications section. You know, when you hear the ad for the drug, it will say, "Lofexidine is approved for this." As we went through our review, we started appreciating how interwoven they were and wanted to get a better understanding of are these really two different things or is one of them just a confirmation that the drug is doing what it purports to do, which is to make people more comfortable to mitigate symptoms of opioid withdrawal. That's the nature of the question.

There is some flexibility and lack of consistency in what goes into indication statements and what doesn't. On the one hand, you don't ordinarily put everything that the drug does into the indications section of the labeling. There could be lots of effects of a drug that aren't its indication. But sometimes you do pull things out distinctly, especially if there are some drugs that do one thing and some drugs that do three. This is

basically what we wanted to explore not necessarily just for this drug but for other drugs that might be developed for this same type of problem.

Does that help?

MS. NUMANN: Yes. Thank you.

DR. NARENDRAN: Dr. Proschan?

DR. PROSCHAN: I guess I don't see the harm with including that as a second indication because I think they have shown that. I agree that they are interrelated, but I think the data supports that as a conclusion as well as ameliorating the symptoms.

DR. NARENDRAN: Dr. Conley?

DR. CONLEY: Yes. Thanks. I guess I have a question back to the FDA from this just to kind of help from an industry standpoint as we develop these things. It's hard to imagine, for anything in a sense, that when you have something that's only going on for 5 or 7 days, that something that might make you feel better continues to help you do something for a short period of time. So I get it that there's probably no way to tease those two

apart. But what I do actually wonder, kind of more of a question, is how useful do you see having a label drug?

That to me goes along with how many claims are being made for it or whatever. This is one where if there's an obvious -- it's conflated, but maybe it doesn't hurt anything I guess is what I was hearing you say. I get that. I'm not trying to advocate for it. I'm actually just kind of asking because there are a lot of these old things out there that we could develop more. To me, this is a pretty good example of doing that.

Clonidine was around for a long time. There's been a lot of usage of it, and I guess I wanted to partly get that statement out there before we go into all these other questions, is to understand, is part of your interest in this is how useful is this? Because I would see that as we go into the future, there will be more studies and more understanding about whether these things go along with each other or not, and I can see having more in a label may be leading to studies like

that, where if it's super narrow, won't lead to it.

But I'm actually not sure what you all think about that, whether you think it's useful to have a labeled new version of kind of an old idea, because this is novel and not novel at the same time. So I just wondered about that.

DR. HERTZ: I'm not sure I completely understand what you're asking, so I'm going to try and ask you back, and you tell me if this is the right question to answer.

In the context in which something of a similar class has been used for decades, what is our interest in having a product label for the actual use?

DR. CONLEY: I tend to go on, but that's actually the question. Thank you very much.

DR. HERTZ: I think that it's always a good idea for products to have labeling that reflect clinical indications or uses that are important to the medical community and patients, and that while the practice of medicine exceeds beyond what we have captured in drug approvals and labeling, and

that's a good thing, that doesn't supplant the value of actually having data supporting a product and having all of that in the label.

I don't see the one necessarily having -- like the old uses, that alone is not necessarily good enough if somebody is able to go beyond that, have a very clear database, coming with the studies, the data, the application, and have it formally reviewed and then a decision made.

DR. NARENDRAN: Dr. Brady?

DR. BRADY: This is Kathleen Brady. If I take this question very literally, the appropriateness of including facilitation of completion of the withdrawal, I think we just don't have the data to address this question because at the end of both the 5- and 7-day treatment, patients were symptomatic in the lofexidine. And we know that in Great Britain, the recommended treatment is I think 12 days. So I just don't think we have the data to talk about completion of the opioid discontinuation syndrome.

DR. NARENDRAN: Dr. Turner?

DR. TURNER: Yes. Erick Turner. I guess I am going to also perhaps nitpick the wording of this question. It's actually two sentences; discuss the appropriateness of including facilitation and completion of abrupt opioid discontinuation treatment as a second indication.

I personally think it should be a separate indication from the separate question of mitigation of symptoms. Yes, to me they are two separate issues. Does that mean I believe the data support that second indication; that's a whole other question. I guess that's question number 2, and I don't see a vote on that particular question down below. I only see one more vote coming, which is overall approval of the application.

So I'm wondering will this be delineated in the labeling if approved as this is a separate issue. And if it isn't felt to meet the threshold for approval, will that negative be clearly stated in the labeling, that it's approved for this but not for that. But just like you do see it in the labeling for other products, is approved for the

acute treatment of a condition but not for the long-term treatment, the efficacy of blah, blah, blah has not been evaluated beyond X number of weeks or months, whatever.

DR. NARENDRAN: Dr. Jain?

DR. JAIN: Felipe Jain. I agree with the prior comments, and I think that the data does support the FDA's endpoint in the trial endpoint of days 5 and 7. Lofexidine does facilitate completion through that time period.

DR. NARENDRAN: Dr. Proschan?

DR. PROSCHAN: I was just going to point out, it does say completion of abrupt opioid discontinuation treatment, so I interpreted that as short term.

DR. NARENDRAN: Ms. Witczak?

MS. WITCZAK: Kim Witczak. I sat doing a literal read of a completion because that's a pretty finite thing. But going back to your comment, Felipe, and what you were just asking about is 5 to 7 days -- sure, that's the data, but is that good enough? That would be my comment.

DR. NARENDRAN: I think I do want to make a comment myself. It's sort of a confirmation of the first thing, which is it does treat opioid withdrawal symptoms. But I feel to add it as a second indication in some way is really confusing. I feel it would be more clear just to say it treats opioid withdrawal symptoms. The concept of opioid discontinuation syndrome can't be pegged at 5 days, 7 days, or 30 days. The protracted withdrawal syndrome has been shown to extend up to 30 days before it could really move to -- so I agree with Dr. Brady that the data doesn't really support this particular worded statement. That's my personal opinion on that.

Are there any other comments? Dr. Carroll, do you want to make a comment?

DR. CARROLL: Yes. Kathy Carroll. Along those lines, again, the word "complete" is so loaded and so impossible in this particular population. In the earlier FDA document that we were sent before, so many people withdrew because of subject request, and this sounds like substance

users, multiple instances of patients saying their withdrawal symptoms were over; multiple patients saying they wanted to go out for a smoke.

So all those funny kind of explanations that our patients come up with fall into completion, and then it becomes a little less meaningful. So I think you can say abrupt discontinuation of opioids up to 5 days. You can either do the time thing or you can do that their symptoms were clarified. But otherwise, it's almost impossible to figure out what completion really means.

DR. NARENDRAN: Dr. Fiedorowicz?

DR. FIEDOROWICZ: Yes. My initial comments were to frame the discussion. I'm going to follow my commentary with that framing in mind. The FDA suggestion to relegate this to the clinical study suggestion rather than conceptualize -- and this is an indication -- resonates with me and thinking of it more as conceptualizing, as confirming that primary outcome.

People have mentioned the idea of not seeing harm and including this indication. I do think

there is potential harm with the use of the word "completeness," which also bothers me and the idea that people could understand we've successfully completed something. We've all discussed and recognized the need for longer term treatment. We have expert opinion in the UK guidelines recommending longer term follow-up and treatment here, and we also had comments about individual differences in course here, and I don't think that we have data that says that this was complete. But also the focus was on really short-term opioids in the pivotal studies as well.

So to say that things are complete within this time frame I think is going to be more difficult when these are likely going to be applied more broadly. So I think there is potential harm in use of the term "completeness," and I also think that it makes sense just to relegate this to a different section.

DR. DUNN: Not to beat on a dead horse, but this term of completion, right, it's very ambiguous, hard to define. I would be much more

comfortable if it just said "facilitation of abrupt opioid discontinuation treatment." That being said, I do agree with the early comments by Dr. Pickar that making these patients more comfortable completing a 5-day and 7-day course probably is a potential proxy that they'll do better long term and reach that completion, whatever that may be, a zero score on the COWS or the SOWS.

I think for these particular studies, for this particular patient population, I think that requires us to make too many assumptions. The study population's idealized, fairly young, and not a lot of medical comorbidities, no comorbid psychiatric medication used, but I think in reality, you're going to see a much more heterogeneous population. And for us to make that conclusion that the results of these studies are going to translate into completion out in the real world is a little bit of a stretch.

So I think without that completion, I would be much more comfortable with this second

indication, but given the ambiguity of it and, again, this difficulty in extrapolating the results in this patient population when we're going to use it in clinical practice makes it difficult to support this second indication for myself.

DR. NARENDRAN: Thank you. So it sounds like, just to summarize the discussion, a couple folks thought there was no harm in including this as a second indication. However, overwhelmingly, a lot of people felt a little bit uncomfortable, the definition saying completion of opioid withdrawal treatment. It felt like it was poorly defined. The treatment sample was an over-idealized sample that may not be as generalizable, longer term data, the 5 to 7 days. It feels like mostly people felt that they would like to see more data to be more convinced before that could be included as a second indication, but there seemed to be support to somehow include this in the package insert. Thank you.

Dr. Pickar?

DR. PICKAR: Let me just understand. Does

that mean that we're voting on two indications separately? When it says do you recommend the approval of this application, does that mean both?

DR. NARENDRAN: That's not a voting. It's just a discussion.

DR. PICKAR: That's a discussion.

DR. NARENDRAN: Just a discussion question.

DR. PICKAR: So the approval of the application is both then.

DR. WINCHELL: You can clarify for us after the vote any limitations you would see.

DR. PICKAR: So the answer is yes. It includes both. Okay.

DR. HERTZ: This is Sharon Hertz. I would take it as this. When you vote whether it should be approved, please vote whether you think it should be approved for mitigating the symptoms in this setting as a minimum of what could be supported as an indication for approval. And then as Dr. Winchell said, if you think that more indication is appropriate for the approval, you can let us know that.

DR. NARENDRAN: So when you explain your vote, you can say you voted for both versus one or just one, sort of.

(Laughter.)

MS. WITCZAK: Kim Witczak. I kind of feel like it has to be two because to say minimally that, yes, I think it does for the symptoms, that still leaves too much leeway that if we don't distinguish it for both, like to say the words -- because it's two different indications, and I see it down the road as a consumer and somebody in advertising and marketing. I can see it being used, and that word "completion" is loaded.

DR. HERTZ: Let's go back to what Dr. Winchell said initially. Vote whether you think it should be approved, and then tell us what you think the indication should be.

DR. NARENDRAN: Question number 4 is a discussion question. Discuss which dosing regimen is best supported by the data given the similarity and efficacy results and differences in toxicity

between the 3.2-milligram and the 2.4-milligram per day doses. Dr. Proschan?

DR. PROSCHAN: This one I think is a lot harder for me because the forest plots, one can get a misleading impression and say, oh, gee look; it helps on all these different things. But those are highly correlated, so it's not surprising that if you see a small benefit on one, you're likely to see a benefit on others. So it's not like those are completely independent things, and I am concerned about the safety difference between 2.4 and 3.2.

I'm also worried that in a trial where they say you can withdraw medications based on the doctor having set criteria, but that's not going to happen in the real world with the patients. So I would worry that you might get more problems like someone falling down the stairs or something like that because of syncope.

So I am actually kind of concerned about the 3.2 dose. On the other hand, I wonder, safety relative to what? Relative to using methadone,

relative to using nothing and having someone perhaps overdose and die? Safety is always relative to something, but I would feel more comfortable about the 2.4 dose.

DR. NARENDRAN: Ms. Numann?

MS. NUMANN: Sabrina Numann. Going along the lines again of this vote and what we're covering here for number 6, if I had the ability to choose between 3.2 and 2.4, I'd feel more comfortable about whether or not I could even vote. So when we do that vote, are we going to be including, A, the facilitation of withdrawal; B, and discuss a second indication; and then C, which dose we are voting for.

I just feel like the final vote is going to be covering a lot of things. If it could be separated, I think that would be a lot easier to be able to get through this process, and that is because I have much -- like what's been discussed, I have a lot of concern about that higher dose. If this entire discussion was just on 2.4, I'd have a completely different feeling. I want to put that

out there, whether it be for future meetings or tonight, it's something to consider.

DR. WINCHELL: We try really hard to write these questions. You might think we just wake up one morning and just blue-sky them, but no, we edit them. There are like 17 people. We edit them again and again, and they're never right.

Let's put it this way. When we get to the vote, if you think there's a dose, an indication for which it's appropriate to approve this application, I'd like you to vote yes. If you think there isn't, I'd like you to vote no. And when we go around, you let us know what you think about the indication and the dose.

DR. NARENDRAN: Dr. Jain?

DR. JAIN: This is Felipe Jain. I find myself surprised that the major class effect of this or class side effect of lofexidine is on the cardiovascular system, and yet I haven't heard anyone describe their self as a cardiovascular physiologist or even a cardiologist. And what I've seen from the side effects, at least at the

3.2-milligram dose, particularly in women, is concerning if 2 out of 64 women are going to the hospital because of bradycardia and hypotension. That's quite concerning.

I didn't see any particular information on rebound hypertension beyond 7 days, but there are some side effects. I should say that a few individuals have had side effects beyond day 6 or day 7, which are correlated with hypertension. For example, a cerebrovascular accident is more commonly associated with hypertension or even caused by hypertension.

So that's concerning to me, and I feel despite the lack of data that we have on rebound hypertension, really, to evaluate in either of the doses, I feel much more comfortable with the 2.4-milligram dose because of the experience within the broader literature, the experience from the UK, which gives me a lot of comfort with that particular dose. But the 3.2-milligram dose, particularly given the practice settings that were in the likely medications that patients receiving

this will be on that may have additive effects on hypotension or bradycardia does make me quite concerned about the 3.2-milligram dose.

In terms of efficacy, it would have been helpful to have seen something like an effect size between 2.4 and 3.2, or a number needed to treat in order to get one more person to discontinuation, something of that level as opposed to simply a trend of results within those forest plots. I feel like we were asked to approve a higher dose that has a clear signal for increased side effects without a clear signal for increased efficacy.

DR. NARENDRAN: Dr. Fiedorowicz?

DR. FIEDOROWICZ: Thanks. My comments are going to be consistent with what people have said. I found, curious as I was reading the materials beforehand and during the presentation, a strong push for 3.2 milligrams per day. Kristen Gullo referred to a trend in favor of that dose, but the word "trend" here is not referring to either a statistical effects trend, where I would use that term, nor is it referring to any effect that

approached clinical significance as was done in the FDA analyses where there were really no differences. There are negligible differences in efficacy between these doses that are not clinically significant by any standard from what I can tell.

There was a 3 to 3 to 2 random assignment in study 3-1, so there's actually power to detect the smaller effect between the two active treatments, and we would expect a much smaller effect between two active treatments. So I think that's what Kristen was referring to, but clearly there's not even very small effects here. These are negligible.

The only compelling piece I can see in favor of that dose was that the reasons for discontinuation, so there did appear to be differences in reasons for discontinuation with a lower dose being more likely to discontinue because of withdrawal symptoms, which makes sense, and the higher dose because of adverse effects. So I kind of liked the idea of including some range here so

that clinicians have the option of treating those who might still be having symptoms at a lower dose of 2.4, but I would worry about a strong push for the 3.2-milligram dose given the greater risk. And particularly I thought that risk may be unduly burdened on women. I was not convinced by the FDA analyses that that was entirely weight related. The weight related stratification did not seem to explain a lot of the differences there.

The other concern that I have is that these studies effectively excluded a lot of people with risk factors for cardiovascular disease whom we know are going to be more likely to have these sort of adverse effects. Study 2 for instance excluded those on antihypertensives, antiarrhythmics, cholesterol-lowering drugs. These are people that have risk factors for or have vascular disease.

I am here primarily as a psychiatrist, but I do want to follow up on Dr. Jain's comments. My research focuses on the cardiovascular side effects of psychotropic medications and cardiovascular risks associated with psychiatric disorders, and

I'm the medical director of a human cardiovascular physiology laboratory.

DR. NARENDRAN: Dr. Jeffrey on the phone?

DR. JEFFREY: Hi. Jessica Jeffrey here from UCLA. [Indiscernible - audio gaps].

DR. NARENDRAN: Dr. Dunn?

DR. DUNN: Walter Dunn. My take away from the sponsor's presentation and FDA's presentation is generally in these studies, 3.2 and 2.4 in terms of efficacy is about equivalent, but that there was a clinically significant increase in the events of bradycardia, syncope, hypotension in the higher dose of 3.2 milligrams. That's even in what was called an idealized population under close inpatient supervision, and again thinking about when this rolls out into the clinic, these are going to patients who were outpatients. They are going to be on other medications that prolong QT. They're going to have a lot more medical comorbidities. So I think that the rates of those adverse events will be much higher than what we see in this study.

That being said, I can certainly appreciate the need for a higher dose to treat more severe withdrawal symptoms, but I think clinically what's going to happen is that physicians are going to go above the FDA recommended dose if it's limited at 2.4 to treat those more serious symptoms. But I think if we only approve the 2.4, that will give clinicians pause to think about all these other risk factors in their patients before going to 3.2

So I think addressing the data here, it's my personal belief that balancing the efficacy and safety data really supports the 2.4-milligram dose, but that in reality, yes, clinically people are going to go up to 3.2. But I think we should give them pause to go to the higher dose because even in this idealized population, we're already seeing the signal that there are more adverse effects at the higher dose.

DR. NARENDRAN: Dr. Brady?

DR. BRADY: Yes. I certainly agree with the general consensus here. It seems to be that the efficacy isn't that different between the two

doses, but the side effects for 3.2 seem to be worse. I would just like to emphasize that I think saying something about flexible dosing would be useful because it does seem like some people did do better on the 3.2 dose. The reasons for discontinuation really were significantly different.

Also, the other end of that is we don't know how low a dose might treat this withdrawal as well. So it's possible I think -- a lot of studies I saw people were using 1.6 milligrams. So I think the idea that the dosing needs to be tailored in some individual way needs to be emphasized.

DR. NARENDRAN: Dr. Turner? Sorry. Go ahead. Dr. Petullo?

MR. PETULLO: I just want to make one comment. In these studies, patients were able to skip dose, and if you look at slide 41 of our presentation, the actual on-average, the mean dose this, the 3.2-milligram dose, they didn't get 3.2, they got 2.5; the same with the lower dose.

DR. NARENDRAN: Thank you for that

clarification. Dr. Turner?

DR. TURNER: I just want to echo I think what Dr. Dunn was saying and a few others about if we look at there being a clear dose response effect in terms of the safety issues, and you see it particularly in FDA slides on page 22 23, and 24, slide numbers 44 through 47, the number of doses withheld in the 3.2-milligram group, 13 percent, and the 2.4 milligram group, 9 percent; and in the placebo group zero. And similar numbers for orthostasis, 14, 8, 0, and a similar trend with orthostasis, and the AE is 42 percent, 29 percent, 5 percent and so on. Some are with bradycardia.

Anyway it's consistent throughout and sort of like replication. So I think there's definitely something there. I agree that clinicians are going to do what they're going to no matter how it's label. Even if you say it's approved up to 2.4 milligrams, then again they can do what they want to do in the other direction, too, and hopefully we'll explore lower doses. Thank you.

DR. NARENDRAN: I'll try to summarize the

discussion. It seemed like overwhelmingly people felt they weren't very convinced about the efficacy at the highest dose, but they would seem to be very convinced that there are more risks at the highest dose, 3.2 milligrams. There was specifically more concern about the dosing for women: cardiovascular disorders, people who may be on comorbid psychiatric medications; and people who may not be abruptly discontinuing.

So there seemed to be a lot in favor of the lower dose. However, there was also -- in some way, if it's communicated that people were tested as high as 3.2, which I assume would be in the package insert, clinicians may have the option to go higher.

Does that summarize the discussion?

(No audible response.)

DR. NARENDRAN: Thank you. So we'll move to question number 5. Discuss the adequacy of the available safety data to support use between 7 and 14 days. Who wants to go first? Ms. Numann?

MS. NUMANN: Sabrina Numann. I have a

safety concern regarding long term, and I know this is not meant for long term. Coming from my perspective, I take this medication for 7 days, and I'm done. My withdrawal symptoms have eased, and I've decided to go into treatment. Then I go out with some friends, and I take an opioid again, and I decide I want to go through that again. I go back to my doctor on day 8 or 9, and I say I need to go back on this another 7 days because I've been using opioids for the last 24 hours.

How many times would they be able to do that? How long can they stay on this medication and worry about these risk factors? I appreciate the 30-day follow-up information, but that was 75 percent, just over a hundred people. And what if all those other people, after they had relapsed, wanted to start it again? These are some of my concerns with regard to long-term use on this. Thank you.

DR. NARENDRAN: Anybody else want to comment?

(No response.)

DR. NARENDRAN: I think in terms of the 14 days seems -- I mean, knowing what we know with how clonidine is used, I think clearly they tested up to 7 days. I feel it's reasonable to think 14 days could be okay. The fact that opioid users go repeatedly back over and over is also not within what we don't -- it's within what we expect for them to be detoxed. And you do label it for acute indications, for depression and medications like that. So I think to say it's been tested up to this percentage of days seems reasonable.

Any other comments? Ms. Witczak?

MS. WITCZAK: Kim Witczak. I know you just said something about depression and how that was originally approved with antidepressants, but as the same thing, that was a small clinical trial. Now you have people on it for years. Some of that's going to eventually come out, but to your point how do we know a month from now, or two months, and is it at a point where it just doesn't even work anymore because they keep coming on and off, I think those are just some things to keep in

mind that we don't have data.

DR. NARENDRAN: Dr. Pickar?

DR. PICKAR: This is very nice conversation. I just want to go back to something Dr. Horn said that I entirely agree with. How about that? When you commented on taking essentially a treatment that has never gone through the regulatory oversight, off-label treatment -- and in our field, in psychiatry, we deal with this a lot all the time. It gives a lot of us pause. The value of taking something, even though it's perhaps widely used, but bringing it to the environment with this kind of regulatory consideration and the brilliance of an advisory committee such as this, it's hugely valuable to the practicing doc. And not many people take a drug that has an off-label presence and move it this way.

I give our sponsors a genuine -- whatever the right word is -- thankfulness I think to the community, and I'd like to see more of that, of drugs that are in practice without the kind of data that we're talking about today. So on that one,

I'm entirely in agreement with you.

DR. NARENDRAN: So if there are no further comments, it seems like people would like to see more data for repeated doses, especially given that opioid use goes through multiple relapses, although 14 days seems reasonable as well.

We'll move to the next question. Question number 6 is a voting question. Do you recommend approval of this application? Same thing with the voting question. Please press the button on your microphone that corresponds to your vote. We'll have approximately 20 seconds to vote. Press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or if you wish to change your vote, please press the corresponding button again before the vote is closed. After the vote, we'll go around and discuss the vote further.

(Voting.)

MS. BHATT: The voting results, yes, 11; no, 1; abstain, zero; and no voting zero.

DR. NARENDRAN: So we'll start with this

side of the table. Dr. Fiedorowicz, you want to explain your vote?

DR. FIEDOROWICZ: I recommend approval based on the focus on first indication of mitigated symptoms associated with the additional word "abrupt" opioid withdrawal, but recommend relegating facilitation of completion indication to the clinical study suggestion, as suggested by the FDA. I do feel more comfortable, as I think many of my colleagues do, with the 2.5-milligram per day dose as the recommended dose, but keeping the option of going to 3.2 milligrams per day for persistent withdrawal symptoms.

In spite of this dose being included in only one of the pivotal trials, when you look at the actual doses received in the studies, I do feel comfortable with recommending that lower dose as well.

DR. DUNN: Walter Dunn. I voted yes for approval with the limitation that it only be for mitigation of symptoms associated with opioid withdrawal. Again, I felt that the statement of

completion of abrupt opioid discontinuation was a little bit strong and poorly defined, and the data didn't support that, but perhaps additional studies postmarketing could address that question.

Based on the safety data, I supported for the use at the 2.4-milligram dose, but given the clinically significant increased side effects seen at 3.2 in this idealized population, I felt that the risk-benefit only supported the 2.4-milligram dose.

DR. JAIN: This is Felipe Jain. I voted yes for approval. I voted yes both for mitigation of symptoms and also for facilitation of abrupt opioid discontinuation. I agree with the concerns about completion, and yet at the same time, looking at the SOWS, I don't believe that the SOWS represents opioid discontinuation. It represents that and a whole lot of other things.

I would venture to guess that the average range of symptoms on the SOWS in this audience is somewhere between 1 and 3, which is about where the participants on average ended up by day 5 or day 7.

So it's really quite clear that the very high level of symptomatology that they were experiencing early on in the process of withdrawal from the opiate had reduced to, at least on average, what I think would be about a normal level or possibly slightly higher than normal.

I'm not going to spend too much time going into my concerns, which I already expressed about the 3.2-milligram dose, but I am in favor of the 2.4-milligram dose and believe that this will be a useful option for my patients to receive. Thank you.

DR. NARENDRAN: Raj Narendran. I voted yes for the mitigation of symptom withdrawal and for the 2.4-milligram dose.

We'll give Dr. Jeffrey a chance. Dr. Jeffrey?

DR. JEFFREY: Yes. Hi. Jessica Jeffrey, UCLA. [Indiscernible - audio gap].

DR. TURNER: Erick Turner, and I voted yes with a caveat that it's for the mitigation of symptoms and not for the facilitation of completion

of abrupt opioid discontinuation. I would just add one thing. Rather than relegate that to the clinical studies section of the labeling, my sense is that clinicians don't read the labeling in general, and if they do read the labeling, they don't go in the clinical study section. They're much more likely to read the dosage administration section, which is usually short and sweet, and it's something that should be made clear in that section that it is not produced for that second indication.

DR. PICKAR: I voted yes, certainly for the treatment of symptoms. I would have not have voted for the second indication. I think everybody's talked about that a lot. I happened to like the 3.4 milligrams. I like a little clinical flexibility, so -- maybe I'm wrong -- I don't have a big beef with that. So really the second one, the first, and the third are all good with me.

MS. WITCZAK: Kim Witczak. I voted no for kind of the opposite reasons of people here, which was yes, and then caveat. I did no because of the literal question. I did think there was evidence.

I do like the idea, and I applaud the company as well as the FDA because I know it's a huge problem.

So I like the idea of helping with the mitigation of symptoms of abrupt discontinuation, but I voted no for other reasons because I feel like there's not enough data. I think long term, the safety, the heart, once again, it gets into the real world, and I again look at it. I come from a marketing background. I can see it, and I'm concerned with the marketing aspect and how it gets communicated to the public, and we still don't have enough data.

But I do applaud -- because I know it's a huge project and an issue. And I also want to go back -- and I know this is kind of setting the stage. And if I look back to the people here in 1991 at the antidepressant hearings, that kind of set the stage. And there at the same time was the AIDS crisis where there was a lot of public pressure. So I want to just make sure that we're doing the right thing. So hence, my answer, no.

MS. NUMANN: Sabrina Numann. I did vote yes

with the understanding that the efficacy I feel is supported, abrupt withdrawal symptom management, and yes for the 2.4-milligram dose. I don't have enough background to decide whether or not the second dose should be available for increase, but I definitely do not agree that that should be a second indication for completion factors. Thank you.

DR. PROSCHAN: I'm Mike Proschan. I voted yes, but I would make it for the 2.4-milligram dose. I still have concerns about the 3.2, the safety. Again, I'm not an expert on completion, but I do know that you need to complete the first step before you can do the long term. So again, I think if it's made clear that it's for completion of short term, short-term completion, I think that that should be part of the label.

DR. BRADY: Kathleen Brady. I voted yes for mitigation of symptoms associated with abrupt opioid withdrawal and not for the completion of discontinuation treatment, and I think the 2.4 dosage is the correct one to start with.

DR. CARROLL: Hi. Kathleen Carroll. I also voted yes for the symptom mitigation and abrupt withdrawal. It does seem like there's plenty of room for physicians to have a range of doses, but starting more conservatively probably makes sense. I already discussed all the complications about completion, but I also know that just completing one detox successfully probably predicts nothing about the long-term course of the opioid treatment. It's just far too complex, and too many detoxes are usually required, but at the same time, anything that helps, and you never know which detoxification is going to turn the tide for somebody.

DR. NARENDRAN: We'll move to our last question, question number 7. It's a discussion question. Discuss any issues that should be evaluated using postmarketing requirements. Whoever wants to start is fine. Dr. Turner?

DR. TURNER: Yes. I'm concerned about the issue of rebound because there's very little data on that, and it sure is happening all the time with clonidine already in the real world, but we just

seem to know very little about it. If we don't look at it, I think there could be a certain irony here in that we are in this place because we've underestimated the issues of short-term treatment with opioids, that too many people become dependent before we know it, people being sent home from hospitals and offhand being treated with opiates and not being told a thing about what to expect.

I'd hate to see something similar occur with clonidine, that we're creating rebound hypertension. And perhaps once it's out there and being taken by millions of people -- and perhaps increased use of clonidine as a result of the marketing of this drug if approved, then perhaps more cases of sequelae such as CVAs as a result of rebound.

That's the main point, lower doses, exploration of the efficacy and safety -- well, safety is less of a concern. It would be nice to have numbers on it, but also numbers on the efficacy. And then finally, just an education point, maybe getting the word out if it could be an

effort on the part -- it seems like patients are being sent home with opiates, again, not being told a thing about what they could be getting themselves into. And perhaps if there could be -- make this more of a broader public health issue of do they know what they're -- maybe they should be thinking about this class of drugs. Thank you.

DR. NARENDRAN: Anybody else have any comments? Dr. Dunn?

DR. DUNN: Walter Dunn. I just want to point out the issue of the QT prolongation again. Once this rolls out into the clinic, our patients are going to have a lot more cardiovascular comorbidities. They're going to be on medications that also prolong QT. I'm thinking in particular about antipsychotics, which are being widely used for indications other than psychosis. I imagine that a good number of our patients are going to be on an antipsychotic, which they can also prolong QT, so that in addition to this potentially acting synergistically.

Additionally, my impression is that the

majority of opioid detoxification does not happen in the abrupt setting, and that really it is a tapering process, and those opioids themselves also prolong QT. So I think monitoring for complications associated with QT prolongation should be something that is monitored after it's approved.

DR. NARENDRAN: Dr. Jeffrey on the phone?

DR. JEFFREY: Yes. Hi. Jessica Jeffrey from UCLA. I have a question for postmarketing [indiscernible - audio gap].

DR. NARENDRAN: Thank you. Anybody else?

(No response.)

DR. NARENDRAN: No other questions?

(No response.)

DR. NARENDRAN: I also am concerned a little bit that people will -- I know they use it in an idealized setting inpatient. They gave them zolpedem for insomnia. Typically, people are not going to give addicts zolpedem to go. They're probably going to write trazodone, or Remeron, of Seroquel. So I'd be more concerned about some of

those medications with a cardiovascular risk, so that would be critical to know.

Also, the people who are actively using, I want to stress that as well because people are going to be using heroin to kind of supplement their withdrawal symptoms a little bit and try to cross-taper themselves when they go home.

Any other comments?

(No response.)

DR. NARENDRAN: Just to summarize, I heard that people would like to see postmarketing studies characterizing the rebound hypertension risk, QTc prolongation with other antipsychotics and psychiatric medications. They'd like to see studies where people cross-taper from prescription opioids as well as from methadone rather than abruptly be transitioned to this; and also studies in adolescents and children who potentially could be on other psychiatric meds for ADHD.

If there are no further questions, we'll adjourn this meeting. Any last comments from the FDA?

DR. HERTZ: Thank you. It's always helpful to hear your thoughts on these topics, and we will think very carefully about everything that was said as we do our deliberations for this action. Thank you.

Adjournment

DR. NARENDRAN: Thank you. Panel members, please leave your name badge here on the table so that they may be recycled. Please also take your personal belongings with you as the room is cleaned at the end of the meeting day. Meeting materials left on the table will be disposed of. We will now adjourn the meeting.

(Whereupon, at 3:11 p.m., the meeting was adjourned.)